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ANNALS of ALLERGY

PUBLISHED BY THE AMERICAN COLLEGE OF ALLERGISTS

Fall Instructional Course in Allergy
College of Medicine, University of Cincinnati
November 3-8, 1947

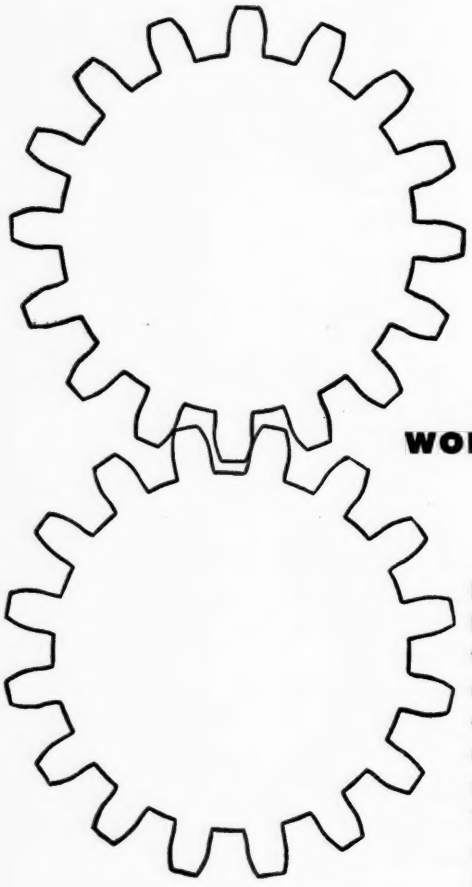
American College of Allergists
Fourth Annual Session
New York City—March 12-14, 1948

July-August

1947

olume 5, Number 4 **Published Bimonthly**

ANNUAL SUBSCRIPTION $6.00 SINGLE COPIES $1.50



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ANNALS of ALLERGY

Published by the
American College of Allergists

Volume 5 July-August, 1947 Number 4

STANDARDIZATION OF POLLEN EXTRACTS

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THE METHOD

THE potency of a pollen extract may be determined in terms of standard pollen units, by the following method:

Standard Pollen.—A stated amount of pollen, known to have been collected properly from several widely scattered sources, correctly identified, and to be practically pure, is desiccated completely and stored in air-tight containers, as the standard of reference. It is designated as the Standard Pollen of assigned number for its species and year of collection.

Perpetuation of the Standard Pollen.—Since it has not been proved that pollen, prepared and kept according to the above-mentioned method, maintains its potency perpetually and since dwindling from use is inevitable, the standard pollen is to be restored each year by withdrawing 25 per cent of it, including that which has been used, and replacing it with an equal amount of fresh pollen. The fresh pollen shall be of the same species, collected from several different sources at the last flowering season and shown to be of the same or greater potency than the standard of the previous year. The mixture of the two batches of pollen then becomes the current standard and is so designated by a new number. The unused pollen that is withdrawn is kept for testing at a future date for possible deterioration.

Preparation of Standard Extracts.—Weigh out 2 gm. of fat-free and completely desiccated standard pollen. Extract in 20 c.c. of Coca's solution for twenty-four hours with occasional shaking at 5 to 10° C.

Filter off the extract through Whatman No. 2 filter paper, 7 cm. diameter, with suction. Measure the volume and restore it to 20 c.c. by flowing the

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necessary amount of Coca's solution over the filter cake and continuing the filtration.

Allow the filtrate to stand seven days at 5 to 10° C.

Sterilize by filtration with diminished pressure through a Seitz (Republic Filter, Inc.) filter pad, Serum No. 1 sterilizing, size No. 3 (35 mm. diameter) used in Seitz filter, improved laboratory model, Size A.

Withdraw a sample for Kjeldahl nitrogen determination and immediately add to the remainder an equal volume of sterile glycerine. Prove sterility.

Calculate the number of nitrogen units per cubic centimeter (0.00001 mg. nitrogen=1 standard pollen unit). The extract is suitable for purposes of standardization for one year if kept without dilution in air-tight containers at 5 to 10° C. It is designated the *Standard Extract* for the species of pollen from which it was made and bears the number of the standard pollen followed by the number of the extraction.

Its potency is stated in terms of *standard nitrogen units* per cubic centimeter, separately determined for each Standard Extract. To this extent the standardization is chemical. Extracts prepared for diagnostic and therapeutic use are assayed on their physiologic activity, regardless of their nitrogen content which need not be known.

The physiologic measure of the potency of a pollen extract is deemed to be its ability to neutralize the homologous reagin of human serum. Standardization of extracts is done by comparing their reagin-neutralizing capacity with that of the standard extract at comparable sites on the same recipient. Their potency is expressed in terms of the standard nitrogen units of corresponding activity, not of their own.

To this extent the standardization is physiologic. Although expressed in terms of nitrogen units, it actually is a measure of reagin neutralization capacity and, as applied to the working extracts, the unit thus becomes a reagin-neutralizing unit.

The Serum.—The serum must be from a donor known to be skin-sensitive to the pollen to be tested. It is desirable that the serum be as highly reaginic as possible to permit dilution at the time of use and because there is evidence that the more highly sensitive serums permit more accurate comparisons.

Dilution of the Serum.—The concentration of the serum and antigens used in the test must be adjusted to give a suitable range of reactions, since neither excessively small reactions nor those approaching the limits of the recipient's response are suitable for accurate comparisons. The object is to find the concentration of serum which, as it is completely neutralized at a sensitized site, gives a reaction below, but not far below, the limit of response of the average recipient. This may be done by *in vivo* or *in vitro* neutralization of serum dilutions by the standard pollen antigen solution at constant strength.

In Vivo Neutralization.—The serum is diluted with normal saline solution without preservative in a series progressing by an arbitrarily chosen common ratio. The choice of ratio depends upon the sensitivity of the serum and the number of sites to be used in the test. Only the most sensitive serums will sensitize in dilutions beyond 1:1,000, and useful dilutions seldom are found beyond 1:500. Consequently, unless the serum is known to be unusually sensitive, about 1:500 is set as the lower limit of the trial dilutions. If six sites are to be used in the trial, the common ratio of 3.5x is satisfactory giving the dilution series, 1:1,* 1:3.5, 1:12.25, 1:43, 1:150 and 1:525. Six sites are *sensitized* with these six serum dilutions by injecting endermally 0.05 c.c. of each.

After twenty-four hours or longer, each site is *tested* by injecting it with 0.01 c.c. of standard pollen extract of selected concentration (about 100 units per cubic centimeter). The average diameter of the wheals of the reactions and of the erythemas including the wheals are measured and recorded. If co-ordinately plotted in terms of cutaneous reaction units,† these may show the vanishing dilution of the serum and the reaction ceiling for the antigen concentration used.

Twenty-four hours later the sites are *retested* for their residual sensitization with a solution of the standard antigen five or more times as strong as that used in the first test. The weakest concentration of serum to give a reaction on the retest is regarded as the neutralization point of the serum for one-fifth of its volume of the selected concentration of pollen extract. Due to the large common ratio (3.5x) necessarily used for the dilution series in the first trial, this figure for the neutralization point is only approximate. It may, however, be used as the lower limit of concentration to narrow the range of dilutions for the next trial.

In Vitro Neutralization.‡—Dilutions of the serum are made as before. Each, then, is combined with an equal volume of 100-unit standard pollen extract and the mixtures are allowed to stand at room temperature for one-half hour. This time-lapse is introduced here merely for convenience in assembling materials and preparing the recipient and has no other significance. However, there is evidence of some deterioration in the diluted antigen even in this short time, hence the time-lapse must be standard procedure.

Six sites are prepared by injecting them with a chosen amount (0.05 to 0.1 c.c.) of each of the serum-antigen combinations. Though these injections are really tests, as well as sensitizations, the reactions which occur generally are too irregular to be of any quantitative significance and are disregarded.

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*The dilutions are expressed as the proportion of serum to the dilution volume. Hence 1:1 indicates undiluted serum.

†The number of cutaneous reaction units $(N)=(e \cdot w)w/10$, where $e=$ the over-all diameter of the erythema and w the diameter of the wheal.

‡The expression, *in vitro* neutralization, is accepted nomenclature and here is not intended to imply that neutralization takes place prior to injection of the materials.

Twenty-four hours, or more, later the sites are retested for residual sensitization by injecting them with 0.01 c.c. of the standard pollen extract of five or more times the initial strength. As before, the lowest strength to give a reaction is regarded as the neutralizing point. The answer should be the same, or nearly so, by either method.

The *in vivo* method has the advantage of giving useful first-test reactions but a great disadvantage in requiring the accurate measurement of 0.01 c.c. in the critical test injections, an operation which has been found virtually impossible with the apparatus obtainable. The *in vitro* method has the disadvantage of almost completely sacrificing the first test reactions but the advantage of requiring the accurate injection of not less than 0.05 c.c. in the critical test. A high degree of accuracy is not necessary in the retest injections since the antigen is used in excess.

From either one of these trials, the range of serum dilutions requiring further investigation can be selected. The appropriate common ratio is calculated to construct a series of six dilutions within the limits chosen. Usually the common ratio will be less than 2x, which is closer than necessary for the purpose required. Serum dilutions are made in this series and tested by means of *in vitro* neutralization by equal volumes of the standard pollen extract of the same concentration as before. The reactions are measured and plotted in terms of their cutaneous reaction units. If the range has been properly chosen, the reaction curve will rise from approximately 0 and begin to level off before reaching the undiluted serum concentration. The levelling off region includes the optimal dilution of the serum for use against the standard pollen extract in concentrations at and below that used in the trial.

This serum-antigen ratio is a characteristic of the serum, relating it to the standard antigen and need only to be determined once. In actual practice the serum may be diluted more or less than this figure, but if this is done the concentration of standard antigen must be raised or lowered in the same proportion in order to be used with it. The only reason this ratio between the serum and extract cannot be used directly for measuring the serum-neutralizing capacity of the extract, thus using the serum as the standard, is that it varies with different skins and there are no standardized recipients. The problem must be approached indirectly.

Standardizing the Working Extract.—The appropriate dilution of the serum is made. The standard extract is diluted with normal saline solution without preservative in a series progressing by a common ratio, depending for its magnitude upon the range that the series is desired to cover and the number of sites to be used. The range is chosen to cover the probable difference between the standard and working extracts. If no information is available regarding the working extract, a preliminary trial is made to discover the approximate relation between it and the standard. For this purpose a series of dilutions of the standard with a common ra-

tio of from 3x to 5x is adjusted so the highest concentration is just strong enough to neutralize its site. Exactly the same dilutions are made of the extract to be standardized. Each antigen-dilution is combined with an equal volume of the diluted serum and, after thirty minutes at room temperature, they are used to prepare sites by injecting 0.05 c.c. endermally. The dilutions of the standard are placed at selected sites on one arm and those of the working extract at symmetrically opposite sides on the other arm of a normal recipient. The immediate reactions are recorded for what value they may have in detecting variations in skin sensitivity. Only rarely do they have real quantitative significance.

After twenty-four hours, or more, all sites are tested for neutralization with 0.01 c.c. of the standard antigen at a concentration in excess of the highest used in the first test. By comparing the reactions of the two series, those which correspond can be found with an error not greater than the common ratio of the series.

For the final trial, the standard is diluted to equal the approximate concentration of the working extract as found in the preliminary trial. Then from each is made a series of dilutions, using a small common ratio. That of 1.75x has been found to be the smallest to give reliable differentiation in a series of six tests.

Each dilution is mixed with an equal volume of diluted serum and used to prepare a series of sites which are retested twenty-four hours later, as before. Since this is the final trial, it is done in duplicate and it is necessary that the results of the two are the same. Otherwise they must be repeated.

Both the test and retest reactions are read and their cutaneous reaction values plotted. From the corresponding points on the two curves are found the relative strengths of the two within an error of not more than the common ratio of the dilution-series.

Standardization also may be done by *in vivo* neutralization. The *in vitro* method is preferred for the reasons already stated. Moreover, it requires one-third fewer injections. Similar results also may be obtained by serially diluting the serum and comparing on the dilutions the neutralizing effect of constant amounts of the standard and unknown antigens by either *in vitro* or *in vivo* neutralization.

APPLICATION OF THE METHOD

Standardization of Sagebrush Pollen Extract

Determination of the Serum Concentration by In Vivo Neutralization.—Serum KP was obtained from a hay-fever patient known to be clinically sensitive to sagebrush pollen and giving a 4 plus reaction to a 20,000-unit solution of it by scratch test. Six dilutions were made from this serum, progressing by a constant ratio of 3.5x. Six sites on the upper arm of a normal recipient were sensitized by endermal injection of 0.05 c.c. of each dilution.

Twenty-four hours later each site was tested with 0.01 c.c. standard sagebrush, 100 units per cubic centimeter. All sites reacted (Table I). That of dilution 1:525 had a value of only 2.1 cutaneous reaction units.

TABLE I. FINDING APPROPRIATE SERUM DILUTION BY IN VIVO NEUTRALIZATION

271		Serum K.P. Recipient R. P. W.					
Site Nos.	Serum Dilus. Ratio 3.5 x	Test: Sagebrush Stand. 100 u.p.c.c.			Retest: Sagebrush Stand. 500 u.p.c.c.		
		W	E	Cru.	W	E	Cru.
1	1:525	7	10	2.1	7	0	0
2	1:150	9	20	9.9	7	0	0
3	1:43	9	25	14.4	7	0	0
4	1:12.25	13	25	15.6	6	8	1.2
5	1:3.5	12	25	15.6	11	20	9.9
6	1:1	12	25	15.6	12	20	9.6

Reactions of sites sensitized with 0.05 c.c. KP serum dilutions, tested twenty-four hours later with 0.01 c.c. standard sagebrush No. 64, 100 units per cubic centimeter, and retested three days later with 0.01 c.c. standard sagebrush, 500 units per cubic centimeter. (See Fig. 1).

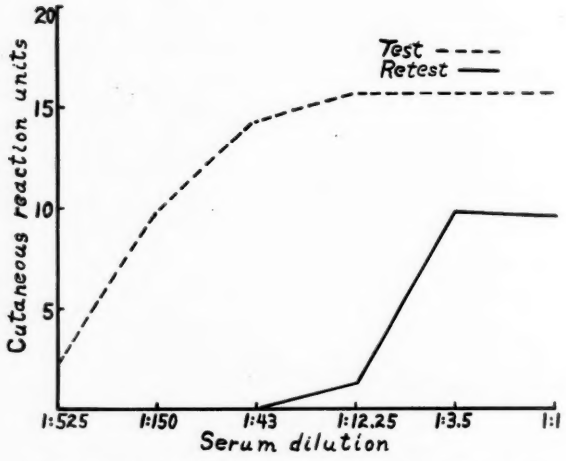

Fig. 1. Reactions of sites of varying sensitization tested and retested with sagebrush pollen extract, as in Table I.

From this the reactions rose to 15.6 reaction units at a dilution of 1:12.25, but beyond this there was no further increase in reaction size with increasing serum concentration (Fig. 1). This is the ceiling or levelling off of the reaction-curve obtainable with 0.01 c.c. of 100-unit sagebrush. To secure larger reactions with the higher concentrations of serum, it would be necessary to use a higher concentration of the antigen.

To discover the degree of neutralization by these reactions, the sites were retested three days later with 0.01 c.c. standard sagebrush, 500 units per cubic centimeter. The sites sensitized with the three lower concentrations of serum showed complete neutralization by the previous injection of sagebrush pollen extract. The site of serum dilution 1:12.25 gave only a borderline reaction of 1.2 cutaneous reaction units. This was the point at

TABLE II. FINDING APPROPRIATE SERUM DILUTION BY IN VITRO NEUTRALIZATION

272A		Serum K.P. Recipient P.B.					
Site Nos.	Serum Dilus. Ratio 3.5 x	Test: Serum Dilus. + Sagebrush			Retest: Sagebrush 500 Units per c.c.		
		W	E	Cru.	W	E	Cru.
1	1:525	12	0	0	5	0	0
2	1:150	10	0	0	5	0	0
3	1:43	13	40	35.1	6	8	1.2
4	1:12.25	14	20	8.4	5	7	1.0
5	1:3.5	12	20	9.6	9	35	23.4
6	1:1	11	20	9.9	9	35	23.4

Reactions of normal sites tested with 0.10 c.c. of dilutions of KP serum in a series progressing by 3.5x, + standard sagebrush, No. 64, 100 units per cubic centimeter, combined in equal parts; and to their retests with 0.01 c.c. standard sagebrush, 500 units per cubic centimeter. (See Fig. 2).

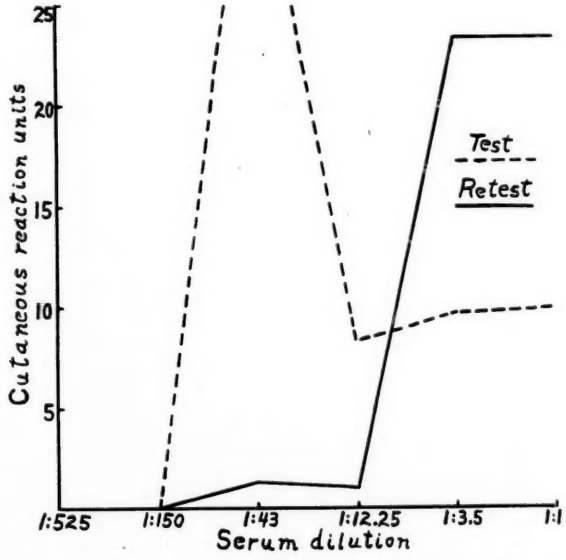

Fig. 2. Reactions of normal sites to combinations of sagebrush pollen extract with varying amounts of homologous serum, and their retests with sagebrush, as in Table II.

which the test curve began to level off (Fig. 1). From this point the reaction size jumped to 9.9 at the site of serum dilution of 1:3.5, but showed no further increase with increasing serum concentration, probably be-

TABLE III. FINDING APPROPRIATE SERUM DILUTION BY IN VITRO NEUTRALIZATION

272B		Serum K.P. Recipient P.B.					
Site Nos.	Serum Dilus. Ratio 1.4 x	Test: Serum Dilus. + Sagebrush			Retest: Sagebrush 500 units per c.c.		
		W	E	Cru.	W	E	Cru.
1	1:21.5	13	0	0	5	0	0
2	1:15.3	9	0	0	5	7	1
3	1:11	13	0	0	5	12	3.5
4	1:7.8	12	13	1.2	7	35	19.6
5	1:5.6	12	22	12.1	7	30	16.1
6	1:4	11	30	20.9	7	30	16.1

Reactions of normal sites tested with 0.10 c.c. of dilutions of KP serum in a series progressing by 1.4x + standard sagebrush, No. 64, 100 units per cubic centimeter, combined in equal parts; and to their retests with 0.01 c.c. standard sagebrush, 500 units per cubic centimeter. (See Fig. 3).

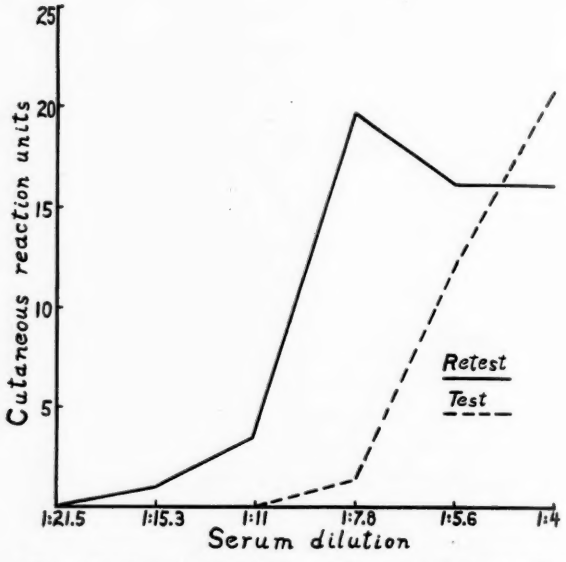

Fig. 3. Reactions of normal sites to combinations of sagebrush pollen extract with varying amounts of homologous serum, and their retests with sagebrush, as in Table III.

cause this is the ceiling for 0.01 c.c. of 500-unit sagebrush. It shows that for use with this concentration of sagebrush the serum concentration must be above 1:12.25 but need not be above 1:3.5.

TABLE IV. STANDARDIZATION OF SAGEBRUSH EXTRACT

277	Standard Sagebrush, No. 64 R.						L.	X Sagebrush						
Stand. Pollen Units Per c.c.	Test: Serum + Pollen Dilus.			Retest: Sagebrush Stand. 300 u.p.c.c.			Site Nos.	Test: Serum + Pollen Dilus.			Retest: Sagebrush Stand. 300 u.p.c.c.			X Pollen Units Per c.c.
	W	E	Cru.	W	E	Cru.		W	E	Cru.	W	E	Cru.	
0	8	0	0	9	50	36.9	6	10	0	0	10	10	30	0
0.32	8	20	9.6	9	50	36.9	1	8	0	0	10	60	50	1.6
1.6	7	12	3.5	9	50	36.9	2	10	0	0	9	50	30.9	8
8	9	20	9.9	8	45	29.6	3	10	12	2	9	45	32.4	40
40	7	30	16.1	8	50	33.6	4	10	20	10	9	40	27.9	200
200	8	20	9.6	6	10	2.4	5	9	15	5.4	9	35	23.4	1000

Reactions of normal sites tested with serial dilutions of standard sagebrush + KP serum compared with those to X sagebrush + KP serum; and as retested with standard sagebrush.

First test: 0.05 c.c. KP serum, 1:8, + equal volumes of dilutions of sagebrush, on the right arm standard and on the left X, progressing by a common ratio of 5.

Retest: Twenty-four hours later all sites tested with 0.01 c.c. standard sagebrush, 300 units per cubic centimeter.

Determination of Serum Concentration by In Vitro Neutralization.—Dilutions of the serum were made as before. Before being injected, each was combined with an equal volume of standard sagebrush, 100 units per cubic centimeter. After one-half hour *in vitro* at room temperature, 0.1 c.c. of the combinations were injected into each of six sites (Table II). The immediate reactions were meaningless beyond suggesting that site No. 3 was more sensitive than the others.

Twenty-four hours later all sites were tested for residual sensitization with 0.01 c.c. standard sagebrush 500 units per cubic centimeter (Table II). The sites of the two lowest serum concentrations were found to be completely neutralized. The 1:43 site showed only a negligible activity and this probably was because this site was extraordinarily sensitive, as indicated by the first test. From the 1:12.25 dilution showing only a trace of reaction, the reaction jumped to 23.4 reaction units but showed no further increase, which essentially was the story told in the previous trial by *in vivo* neutralization. The trial showed, as before, that for neutralization tests with standard sagebrush extracts up to and including 100 units per cubic centimeter, the optimal dilution of KP serum will be found between 1:12.25 and 1:3.5.

To find the optimal dilution more exactly, dilutions of the serum were made, progressing by a constant ratio of 1.4x covering this range and extending somewhat beyond at both ends. The trial was made as before *in vitro* (Table III, Fig. 3). The result showed that the optimal concentration for this serum is about 1:7.8. A dilution of 1:8 was chosen for use with concentrations of standard sagebrush ranging from about 100 units per cubic centimeter downwards.

Testing the Working Extract.—Sagebrush X was submitted for standardization. It was known only to be weaker but believed to be much weaker than standard which was 20,000 standard nitrogen units per cubic

TABLE V. STANDARDIZATION OF SAGEBRUSH EXTRACT

279	Standard Sagebrush No. 64						R. L.	X Sagebrush						
Stand. Pollen Units Per c.c.	Test: Serum + Stand. Pollen Dilus.			Retest: Sagebrush Stand. 500 u.p.c.c.			Site Nos.	Test: Serum + X Pollen Dilus.			Retest: Sagebrush Stand. 500 u.p.c.c.			X Pollen Units Per c.c.
	W	E	Cru.	W	E	Cru.		W	E	Cru.	W	E	Cru.	
0	9	0	0	11	40	31.9	6	10	16	6	11	40	31.9	0
28.82	8	12	3.2	8	40	25.6	1	9	0	0	9	45	32.4	720.5
50.42	9	18	8.1	9	35	23.4	2	9	15	5.4	9	35	23.4	1260
88.23	9	12	2.7	9	30	18.9	3	9	0	0	9	40	27.9	2206
154.4	10	17	7.0	6	15	5.4	4	9	15	5.4	10	40	30.	3860
270.2	10	15	5.0	5	8	1.5	5	9	20	9.9	9	40	27.9	6755

Reactions of normal sites tested with serial dilutions of standard sagebrush + KP serum, compared with those to X sagebrush + KP serum; and as retested with standard sagebrush.

First test: 0.05 c.c. KP serum, 1:8 + equal volumes of dilutions of sagebrush, on the right arm standard and on the left, corresponding dilutions of X sagebrush, at twenty-five times the standard both progressing by a common ratio of 1.75x. (See Fig. 4).

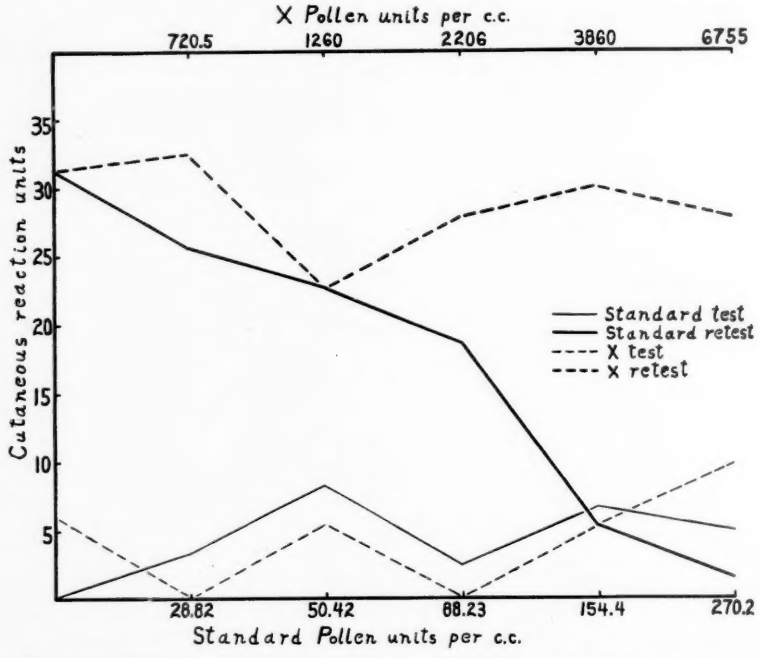

Fig. 4. Reactions of normal sites to combinations of sensitizing serum with standard sagebrush compared with similar combinations with X sagebrush, and to their retests with standard sagebrush, as in Table V.

centimeter. The standard was diluted to 200 standard nitrogen units per cubic centimeter and a series of dilutions, progressing by the common ratio of 5x, made from it. To X was assigned a provisional value of 20,000 X units per cubic centimeter. It was diluted in exactly the same way as the standard. The two series were compared by *in vitro* neutralization on

TABLE VI. STANDARDIZATION OF SAGEBRUSH EXTRACT

280	Standard Sagebrush						R. L.	X Sagebrush						
Stand. Pollen Units Per c.c.	Test: Serum + Stand. Pollen Dilus.			Retest: Sagebrush Stand. 500 u.p.c.c.			Site Nos.	Test: Serum + X Pollen Dilus.			Retest: Sagebrush Stand. 500 u.p.c.c.			X Pollen Units Per c.c.
	W	E	Cru.	W	E	Cru.		W	E	Cru.	W	E	Cru.	
0	7	25	12.6	12	40	33.6	6	8	15	5.6	11	40	31.9	0
28.82	7	25	12.6	8	45	29.6	1	7	25	12.6	8	50	33.6	720.5
50.42	8	30	17.6	8	35	21.6	2	8	30	17.6	8	45	29.6	1260
88.23	7	15	5.6	7	30	16.1	3	9	25	14.4	9	40	27.9	2206
154.40	8	20	9.6	5	9	2.0	4	8	15	5.6	8	35	21.6	3860
270.20	7	18	7.7	5	0	0	5	9	20	9.9	9	40	27.9	6755

All tests as in previous trial, Table V. (See Fig. 5).

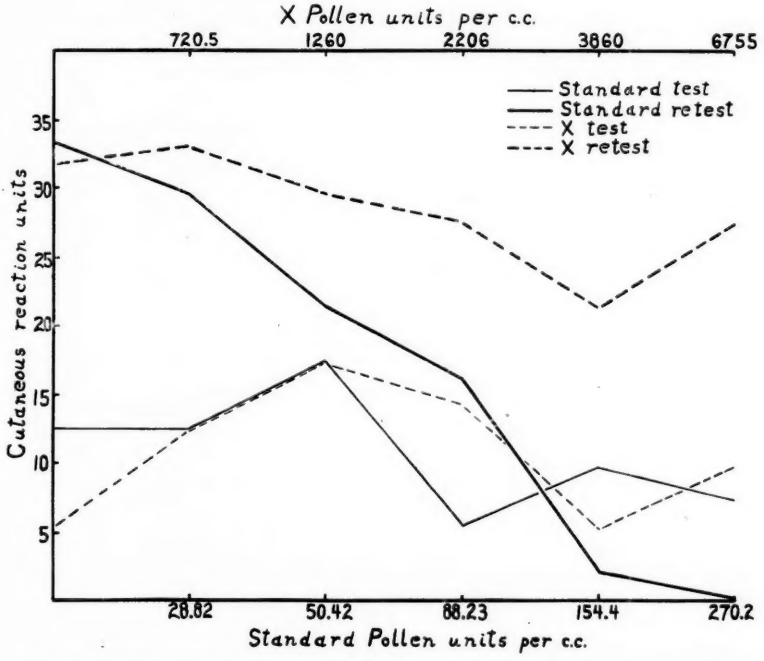

Fig. 5. Reactions of normal sites to combinations of sensitizing serum with standard sagebrush compared with similar combinations with X sagebrush, and to their retests with standard sagebrush, as in Table VI.

opposite arms of the same recipient (Table IV). Retested with 0.01 c.c. of 300-unit sagebrush, the standard showed no neutralization to 40 units. From that point to 200 units almost complete neutralization took place. X was probably starting a similar drop at its full concentration (1000 X units). If so, X was $1/5 \times 1/5 = 1/25$ as strong as the standard. This was put to the test in the next trials (Tables V and VI). In these the standard was diluted in a series progressing by the common ratio of 1.75x

TABLE VII. STANDARDIZATION OF SAGEBRUSH EXTRACT

281	Standard Sagebrush						R. L.	X Sagebrush						
Stand. Pollen Units Per c.c.	Test: Serum + Stand. Pollen Dilus.			Retest: Sagebrush Stand. 500 u.p.c.c.			Site Nos.	Test: Serum + X Pollen Dilus.			Retest: Sagebrush Stand. 500 u.p.c.c.			X Pollen Units Per c.c.
	W	E	Cru.	W	E	Cru.		W	E	Cru.	W	E	Cru.	
0	14	0	0	13	35	28.6	6	7	0	0	13	35	28.6	0
14.41	10	0	0	7	25	12.6	1	5	0	0	7	30	16.1	1441
25.21	10	15	5	7	20	9.1	2	7	0	0	7	30	16.1	2521
44.12	10	0	0	7	20	9.1	3	8	0	0	7	20	9.1	4412
77.2	10	0	0	7	10	2.1	4	10	14	4.0	8	10	1.6	7720
135.1	14	0	0	6	14	4.8	5	12	15	3.6	6	12	3.6	13510

As in Table V, except that the serum concentration is 1:16, one half that used in the preceding trial, and the standard dilutions are also one-half those of the preceding trial but the X dilutions are doubled. These adjustments were made according to the indications of the preceding trial. (See Fig. 6.)

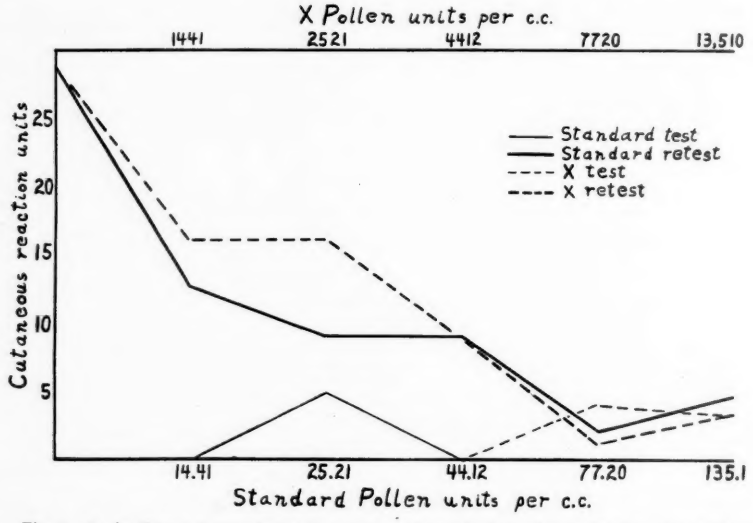

Fig. 6. As in Figure 5 except that the serum and standard sagebrush dilutions are used at half strength while those of X sagebrush are used at double strength. See Table VII.

with maximum concentration at 270.2 units per cubic centimeter. It was estimated that the latter would just neutralize the serum. X was diluted in a similar series, but twenty-five times as concentrated in X units as the standard. In the first trial (Table V), the retests showed that concentrations 6,755 and 3,860 X units almost corresponded to 50.42 and 28.82 standard units, respectively, about three steps apart in the series, but in the second trial (Table VI) 3,860 and 2,206 X units almost corresponded to 50.42 and 28.82 standard units, or about two steps apart in the series. The correct estimate therefore would be between two and three steps in the series. Accordingly, a ratio between the two series of 4 was chosen for the next trial.

It was impossible to increase the X concentration four times because

TABLE VIII. STANDARDIZATION OF RAGWEED EXTRACT

267	Standard Ragweed						R. L.	X Ragweed						
Stand. Pollen Units Per c.c.	Test: Serum + Stand. Pollen Dilus.			Retest: Stand. Ragw'd 1000 u.p.c.c.			Site Nos.	Test: Serum + X Pollen Dilus.			Retest: Stand. Ragw'd 1000 u.p.c.c.			X Pollen Units Per c.c.
	W	E	Cru.	W	E	Cru.		W	E	Cru.	W	E	Cru.	
0	0	0	0	10	50	40	6	0	0	0	10	50	40	0
2	8	30	17.6	8	20	9.6	5	0	0	0	10	45	35	2
10	9	35	23.4	5	7	1	4	10	12	2	9	40	27.9	10
50	10	35	25.0	0	0	0	3	8	20	9.6	9	40	27.9	50
250	9	40	27.9	0	0	0	2	10	30	20	6	14	4.8	250
1250	10	22	12.0	0	0	0	1	10	45	35	2	5	0.6	1250

Reactions of normal sites to standard ragweed dilutions + equal volumes of ragweed-sensitive serum, and their reactions when retested with ragweed alone; compared with X ragweed dilutions treated in the same way. (See Fig. 7).

First tests: 0.05 c.c. of SK serum, 1:5, + serial dilutions, progressing by 5x, of standard ragweed symmetrically opposite corresponding dilution of X ragweed.

Second tests: 0.01 c.c. twenty-four hours later, standard ragweed, 1000 units per cubic centimeter.

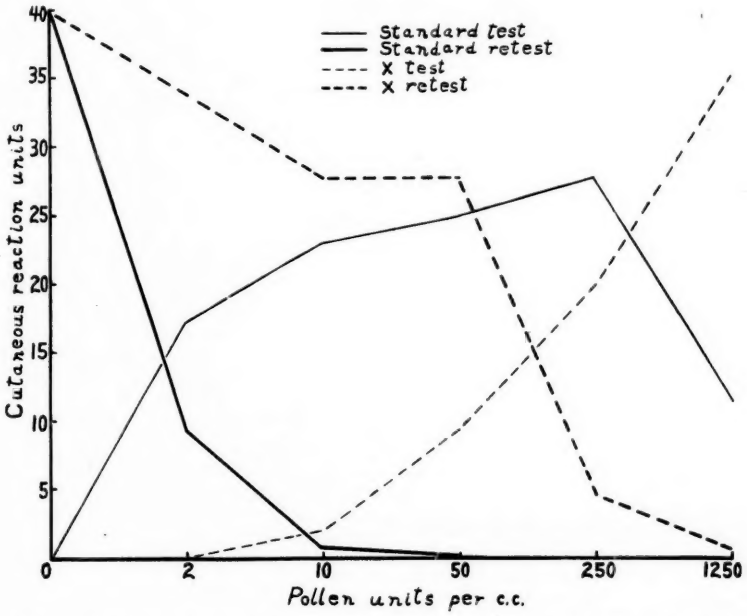

Fig. 7. Reactions of normal sites to combinations of sensitizing serum with standard ragweed compared with X ragweed, and their retests, as shown in Table VIII.

undiluted it was only 20,000 X units. Consequently, X was doubled and the standard was halved. At the same time the serum concentration was halved to 1:16, to maintain the relation between it and the standard which had proved in the two trials to be quite properly adjusted. When these two series of dilutions were tested it was found that X neutralized about the

TABLE IX. STANDARDIZATION OF RAGWEED EXTRACT

269	Standard Ragweed						R. L.	X Ragweed						
Stand. Pollen Units Per c.c.	Test: Serum + Stand. R'gw'd Dilus.			Retest: Stand. Ragw'd 1000 u.p.c.c.			Site Nos.	Test: Serum + X Ragweed Dilus.			Retest: Stand. Ragw'd 1000 u.p.c.c.			X Pollen Units Per c.c.
	W	E	Cru.	W	E	Cru.		W	E	Cru.	W	E	Cru.	
0	6	0	0	12	45	39.6	6	6	0	0	12	50	45.6	0
1.54	8	20	9.6	10	50	40.0	5	6	15	5.4	9	50	36.9	61.6
2.70	7	25	12.6	7	35	19.6	4	8	25	13.6	7	35	19.6	108.1
4.72	8	20	9.6	7	35	19.6	3	6	20	8.4	7	40	23.1	188.8
8.27	7	20	9.1	8	10	1.6	2	8	30	17.6	6	15	5.4	330.8
14.48	7	20	9.1	5	0	0	1	8	30	17.6	5	0	0	579.2

Reactions of normal sites to standard ragweed dilutions + equal volumes of ragweed-sensitive serum, and their reactions when retested with ragweed alone; compared with X ragweed dilutions treated in the same way.

First tests: 0.05 c.c. of SK serum 1:5 + equal parts of serial dilutions, progressing by 1.75x, of standard ragweed symmetrically opposite corresponding dilutions of X ragweed, at 40x standard.

Retests: 0.01 c.c., 24 hours later, ragweed standard, 1000 units per cubic centimeter. (See Fig. 8.)

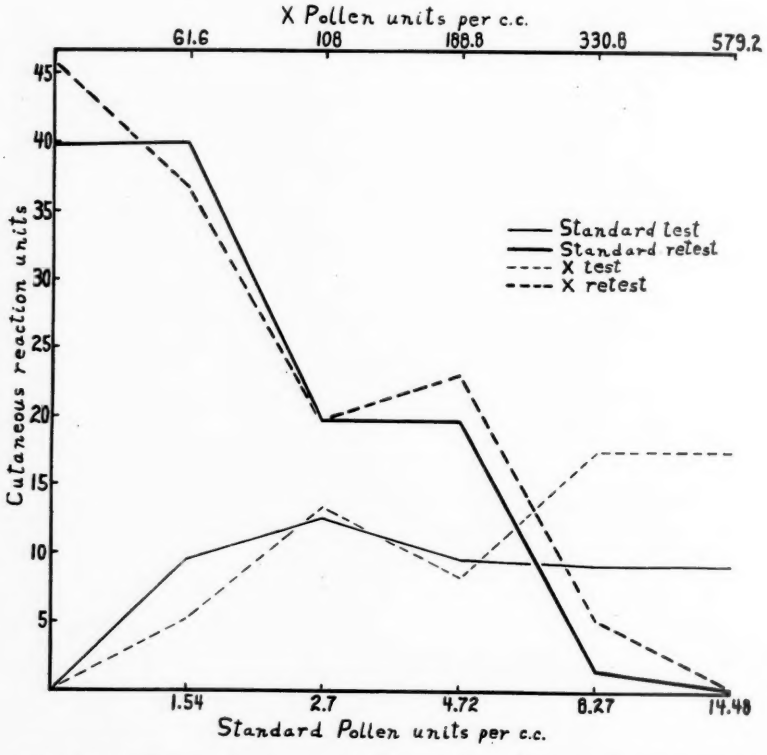

Fig. 8. As in Figure 7, except that the dilutions are in series progressing by the common ratio of 1.75 and those of X 40 times as concentrated as previously, as in Table IX.

TABLE X. STANDARDIZATION OF RAGWEED EXTRACT

270	Standard Ragweed						R. L.	X Ragweed						
Stand. Pollen Units Per c.c.	Test: Serum + Stand. R'gw'd Dilus.			Retest: Stand. Ragw'd 1000 u.p.c.c.			Site Nos.	Test: Serum + X Ragweed Dilus.			Retest: Stand. Ragw'd 1000 u.p.c.c.			X Pollen Units Per c.c.
	W	E	Cru.	W	E	Cru.		W	E	Cru.	W	E	Cru.	
0	7	0	0	10	50	40	6	7	0	0	10	50	40	0
1.54	8	40	25.6	9	45	32.4	5	8	30	17.6	9	50	36.9	61.6
2.70	11	40	31.9	8	35	21.6	4	10	50	40.0	9	35	23.4	108.0
4.72	7	45	26.6	9	40	27.9	3	7	45	26.6	8	25	13.6	188.8
8.27	9	45	32.4	7	30	16.1	2	9	45	32.4	9	25	14.4	330.8
14.48	10	45	45.0	4	15	4.4	1	10	55	45.0	4	10	2.4	579.2

Tests all the same as in Table IX. (See Fig. 9).

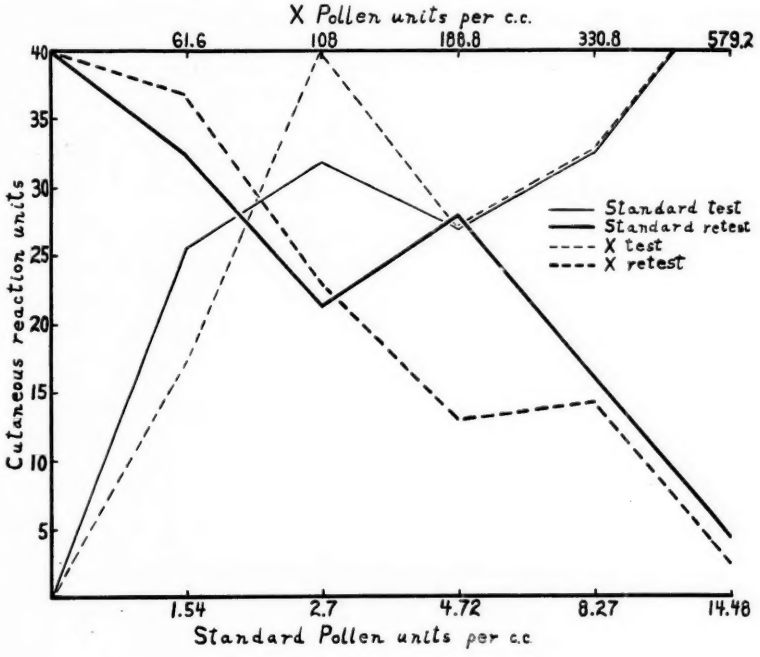

Fig. 9. As in Figure 8. See Table X.

same amount of reagin as the standard (Table VII, Fig. 6). Therefore, in this adjustment which balanced 100 X units against one of standard, the two extracts were of equal potency. It was concluded that X was 1/100 the strength of standard. This was found to be correct. X had been prepared, unknown to the investigators, by diluting the standard 1:10 and again 1:10 by two different investigators not in collaboration.

STANDARDIZATION OF RAGWEED POLLEN EXTRACT

An extract of combined ragweed pollen (tall and short, equal parts) was submitted for standardization. It was known only to be weaker than the standard.

Ragweed-sensitive serum SK was chosen to be used, on the basis of previous experiments, at a dilution of 1:5.

The ragweed standard of 20,000 units per cubic centimeter was diluted in a series progressing by a common ratio of 5x. Ragweed X was assigned a provisional value of 20,000 X units per cubic centimeter, and diluted in the same way as the standard. Both series of dilutions were combined with equal volumes of the diluted serum and the combinations used to prepare sites as before, placing corresponding dilutions of each series symmetrically opposite each other (Table VIII). The immediate reactions suggested that the standard was very much stronger than X. Twenty-four hours later all sites were retested with 0.01 c.c. of standard ragweed, 1,000 units per cubic centimeter, to discover the extent of neutralization. The curve (Fig. 7) showed that X was less than 1/25 but more than 1/250 of the standard; in other words, X was between 800 and 80 standard units of potency and obviously much closer to the former. So, for the next trial X was assumed to be 500 standard units of potency, or 1/40 the strength of the standard.

The standard extract was diluted to 14.48 units per cubic centimeter, which, it was estimated, would just neutralize the sites, and from this was made a series of dilutions progressing by a common ratio of 1.75x. Pollen extract X was diluted to 579.2 X units, that is, 40 times the concentration of standard in terms of X units, and this was diluted in series in the same way as the standard. These series were compared twice, using two recipients (Tables IX and X). In the retests of both trials, the two extracts were found to have neutralized their corresponding sites to approximately the same extent. And when the reactions were plotted coordinately (Figs. 8 and 9) neither curve was consistently above the other; hence the two extracts, as adjusted, were equal, i.e., X was 1/40 the potency of the standard.

Then it was revealed to the investigators that the X extract had been prepared from the standard by diluting it to 500 units or to 1/40 of the standard.

PREPARATION OF A NEW STANDARD

In the ordinary course of events standards must be renewed. The following experiment was done to simulate the procedure for replacing or replenishing the standard by the addition of new pollen, although in this instance standard procedures were not observed in the preparation of the extracts as they would be in actual practice. Two timothy extracts (No. 40 and No. 65) were chosen for comparison. They had been made for experimental purposes at different times, from different batches of pollen,

TABLE XI. ESTABLISHING A NEW TIMOTHY STANDARD

274	Timothy Standard No. 40						R. L.	Timothy No. 65						
Pollen No. 40 Units Per c.c.	Test: Serum + Timothy 40 Dilus.			Retest: Timothy No. 40, 100 u.p.c.c.			Site Nos.	Test: Serum + Timothy 65 Dilus.			Retest: Timothy No. 40, 100 u.p.c.c.			Pollen No. 65 Units Per c.c.
	W	E	Cru.	W	E	Cru.		W	E	Cru.	W	E	Cru.	
0	5	0	0	11	55	48.4	6	0	0	0	11	60	53.9	0
1.87	10	50	40	6	40	20.4	1	10	50	40	6	30	14.4	1.87
3.28	8	30	17.6	7	20	9.1	2	10	50	40	7	20	9.1	3.28
5.73	10	50	40	7	35	19.6	3	9	50	36.9	6	12	3.6	5.73
10.03	9	40	27.9	5	0	0	4	10	50	40	5	0	0	10.03
17.56	9	50	36.9	6	0	0	5	9	40	27.9	5	0	0	17.56

Reactions of normal sites to timothy No. 40 dilutions + equal volumes of timothy-sensitive serum, and their reactions when retested with timothy alone; compared with reactions from timothy 65 dilutions treated in the same way. (See Fig. 10).

First tests: 0.05 c.c. JB serum + serial dilutions of timothy No. 40, progressing by 1.75x symmetrically opposite corresponding dilutions of timothy 65.

Second tests: 0.01 c.c., twenty-four hours later, timothy 40, 1000 units per cubic centimeter.

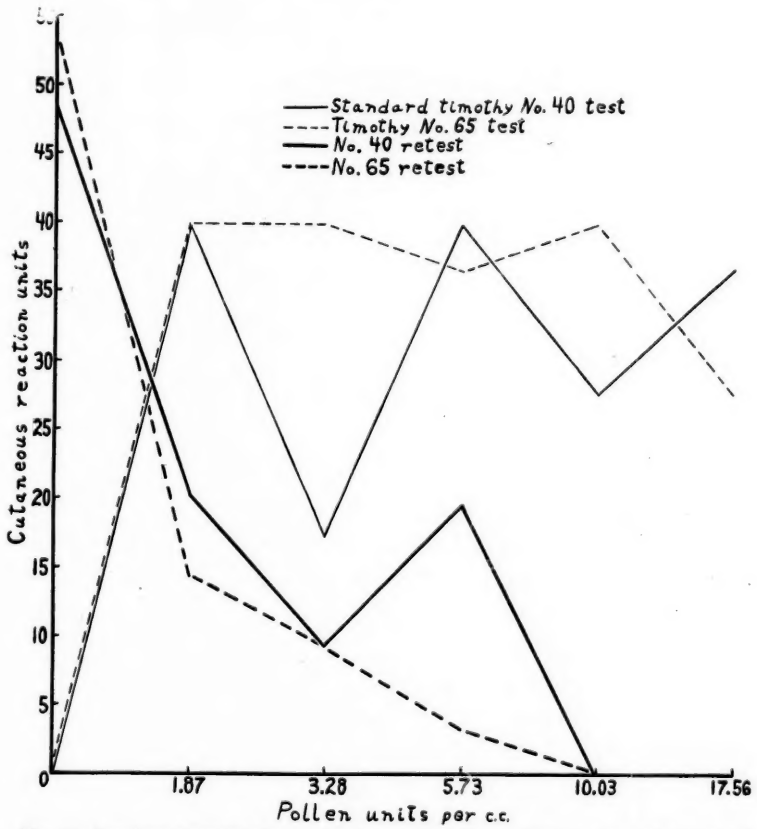

Fig. 10. Reactions of normal sites to timothy standard No. 40 dilutions + equal volumes of homologous serum, and their reactions when retested with timothy alone; compared with reactions of timothy No. 65 dilutions treated in the same way, as in Table XI.

TABLE XII. ESTABLISHING A NEW TIMOTHY STANDARD

275	Timothy Standard No. 40						R. L.	Timothy No. 65						
Pollen No. 40 Units Per c.c.	Test: Serum + Timothy 40 Dilus.			Retest: Timothy No. 40, 100 u.p.c.c.			Site Nos.	Test: Serum + Timothy 60 Dilus.			Retest: Timothy No. 40, 100 u.p.c.c.			Pollen No. 65 Units Per c.c
	W	E	Cru.	W	E	Cru.		W	E	Cru.	W	E	Cru.	
0	0	0	0	10	50	40	6	0	0	0	11	40	31.9	0
0.88	8	20	9.6	7	45	26.6	1	8	30	17.6	7	35	19.6	0.88
1.54	9	20	9.9	8	30	17.6	2	9	35	23.4	7	22	10.5	1.54
2.70	8	35	21.6	7	40	23.1	3	9	35	23.4	7	30	16.1	2.70
4.73	8	30	17.6	7	25	12.6	4	9	40	27.9	6	22	9.6	4.73
8.27	9	40	27.9	6	35	17.4	5	9	40	27.9	5	15	5.0	8.27

Tests the same as Table XI, except that the two pollen series were adjusted to a lower level to get less neutralization of the sites. (See Fig. 11).

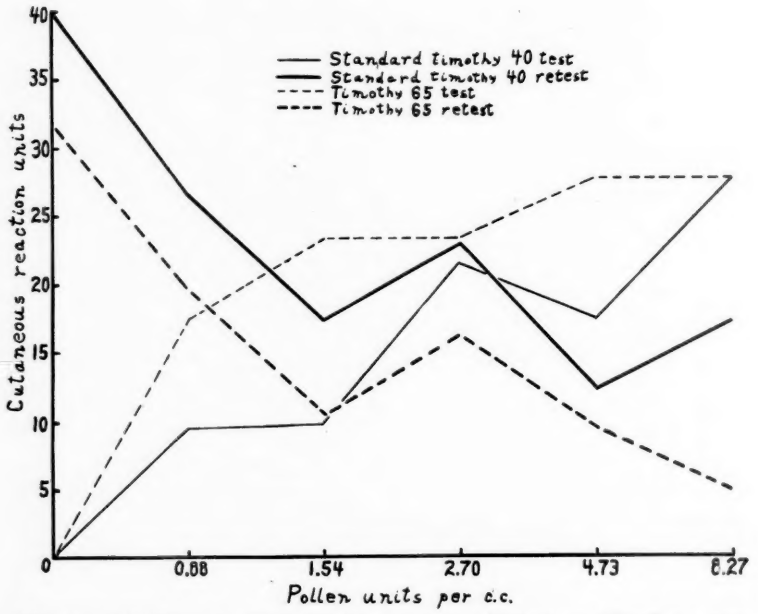

Fig. 11. As in Figure 10, except that the two series of dilutions are adjusted to a lower level to get less neutralization. See Table XII.

and by different techniques. They had in common 20,000 nitrogen units per cubic centimeter and were preserved with 50 per cent glycerine.

Since it was not known if one was stronger than the other, it was assumed that they were of nearly the same potency, and the preliminary trial was made with serial dilutions progressing by the small common ratio of 1.75x. The two series were compared in their neutralizing capacity for a timothy-sensitive serum by *in vitro* neutralization (Table XI, Fig. 10). The first test reaction showed extraordinary irregularities in the right

TABLE XIII. ESTABLISHING A NEW TIMOTHY STANDARD

276	Timothy No. 40						R. L.	Timothy No. 65						
Pollen No. 40 Units Per c.c.	Test: Serum + Timothy 40 Dilus.			Retest: Timothy No. 40, 100 u.p.c.c.			Site Nos.	Test: Serum + Timothy 65 Dilus.			Retest: Timothy No. 40, 100 u.p.c.c.			Pollen No. 65 Units Per c.c.
	W	E	Cru.	W	E	Cru.		W	E	Cru.	W	E	Cru.	
0	9	0	0	10	40	30.0	6	11	0	0	10	40	30	0
0.88	8	25	13.6	6	35	17.4	1	10	40	30	7	30	16.1	0.44
1.54	9	30	18.9	6	30	14.4	2	8	35	21.6	6	30	14.4	0.77
2.70	10	35	25.0	4	12	3.2	3	11	40	31.9	4	12	3.2	1.35
4.73	8	30	17.6	7	25	12.6	4	8	30	17.6	6	25	11.4	2.36
8.27	10	40	30.0	5	11	3.0	5	10	40	30	5	12	3.5	4.13

Tests the same as in Table XII, except that the dilutions of timothy 65 are just one-half those of timothy 40. The trial shows that so adjusted the two extracts are of equal potency; therefore, timothy 65 is double the potency of timothy 40. (See Fig. 12).

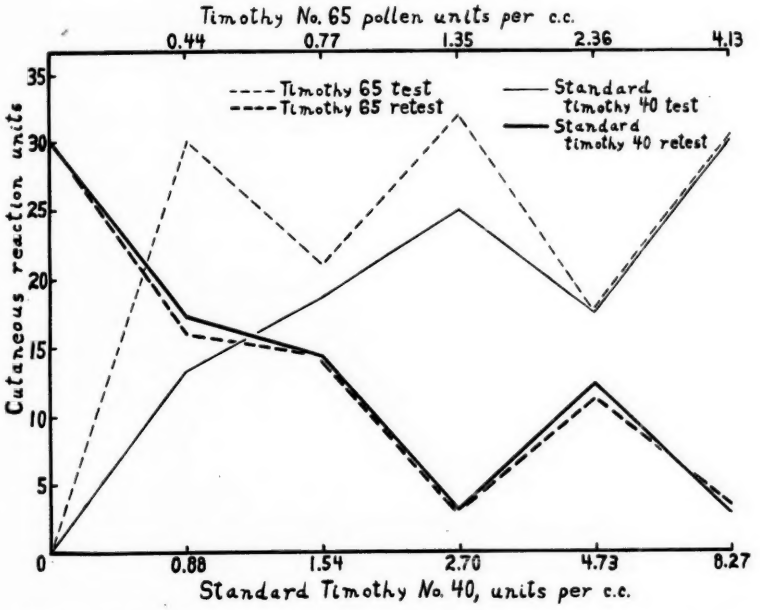

Fig. 12. As in Figure 11, except that the dilutions of timothy No. 65 are one-half those of the standard, as in Table XIII.

arm sites, which were used for the standard series. The retest reactions repeated these rather faithfully, suggesting that they were due to variations in site sensitivity rather than to antigen-reagin reactions. Consequently, this trial had to be largely disregarded. It did, however, show more neutralization in the No. 65 sites than in the No. 40 sites. It also showed that the antigen concentrations had been set too high for this serum concentration, since both extracts gave complete neutralization at 10.03 units per cubic centimeter, rendering the last two sites valueless. From the last

reactions, at 5.73 units, it was estimated that neutralization would probably take place at about 8.27 units per cubic centimeter.

This adjustment was made, keeping both solutions the same, and the trial repeated (Table XII, Fig. 11). In this trial the timothy No. 40 retests were rather consistently above those of No. 65 by a little more than one step in the series. This was best seen by making a tracing of the upper curve and shifting it horizontally to the left until it came as nearly as possible to coinciding with the lower curve. It then was found to occupy a position a little more than one step in the 1.75 series, corresponding to about one-half the unit strength of its present position. In other words, timothy No. 40 had about one-half the neutralizing power of timothy No. 65. This was put to the test by diluting timothy No. 65 to one-half of the unit strength of timothy No. 40 and repeating the trial (Table XIII). It was seen that the corresponding reaction values of the retests were the same, or nearly so, in all cases and when the curves were plotted (Fig. 12) they virtually coincided throughout. Timothy No. 65 thus was shown to be double the antigenic strength of timothy No. 40.

The reason for the different strengths of the two extracts is not known. The experiment is cited only to show the procedure that is necessary in replenishing or replacing an old standard. Presumably such a difference would not be encountered often under standardized procedures.

SUMMARY AND CONCLUSIONS

The physiologic measure of the potency of a pollen extract is deemed to be its ability to neutralize its homologous reagin in human serum.

If a reference standard of dry pollen is maintained and extracts made from it at stated intervals by standardized procedure, they may be used to standardize working extracts of unknown potency by comparing their reagin-neutralizing capacities.

The method employed is *in vitro* neutralization of reagin at local passive transfer sites by dilutions of the standard extract and compared with corresponding dilutions of the working extract. The extent of the neutralization is revealed by retesting the sites with standard pollen extract.

The potency of the standardized extract is expressed in terms of the nitrogen units of the standard extract. Since the potency found for the working extract is that of a dilution of the standard having equivalent reagin-neutralizing value, the unit, as applied to the working extract, is one of reagin neutralization.

This method of standardization is the application of immunologic principles evolved since the discovery of local passive transfer by Prausnitz and Küstner in 1921 and expounded in the works cited below, and to which the writer is entirely indebted.

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(Continued on Page 348)

PHYSIOLOGIC AND ANTIBIOTIC THERAPY OF INTRACTABLE BRONCHIAL ASTHMA

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INTRODUCTION

THE intention of this paper is to present recent experience in the use of physiologic and antibiotic therapy in the treatment of intractable asthma. It should be emphasized, however, that every case of asthma requires careful investigation to determine if possible a specific allergic basis for the condition. Seasonal exacerbation of bronchial spasm is only one of the many points in the patient's history that needs inquiry; thus, the incidence of increasingly severe asthma in some patients in the late fall, after the pollen season, at times is due to the unsuspected circulation of dust from boxed-in radiators when the steam heat is first turned on. In houses with central hot-air heating, dust which has accumulated for years in never-cleaned ducts may be blown into the room through perforated grills in the floor. Food and drug sensitivity should be investigated through the patient's history and later by elimination diets. Every effort should be made to track down the multiple allergic factors which may be involved before physiologic or antibiotic therapy is contemplated.

Intractable bronchial asthma develops in patients who respond to epinephrine, either by hypodermic injection or by inhalation of the nebulin, with only partial and transient relief of bronchial spasm. Many of these patients are successfully controlled for a while by administration of aminophyllin. However, the persistence of allergic stimuli in both extrinsic and intrinsic asthma frequently is responsible for a break through of persisting bronchial spasm, despite continued use of both of these bronchodilator drugs. More and more patients with intractable asthma are observed who have become refractory equally to epinephrine and aminophyllin. They require the employment of methods for bronchial relaxation which permit the gradual curtailment of these bronchodilator drugs (epinephrine and aminophyllin), in order that the patient again may become responsive to them.

PHYSIOLOGIC THERAPY

Of the various methods available, a combination of continuous inhalation of 50 to 70 per cent oxygen and administration of demerol and iodides is the most feasible. Oxygen therapy by means of a ventilated tent, or a rubber catheter inserted in the nasal or oral pharynx, not only

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Presented before the American College of Allergists, San Francisco, California, June 29, 1946.

This study is part of an investigation supported by funds from the Josiah Macy, Jr., Foundation, and, in addition, by a grant from Mr. Cornelius V. Crane, for which the authors wish to express their sincere appreciation.

prevents anoxia but frequently results in a progressive diminution of the severe overinflation of the lungs that characteristically develops in patients with intractable asthma. The diminished pulmonary ventilation engineered by inhaling oxygen-enriched atmospheres gradually permits a more complete emptying of the distended lung, which in itself handicaps the activity of bronchodilator drugs. Saturated solution of potassium iodide in doses of 3 to 4 c.c. daily results in an increased production of mucus, prevention of crusting and, in many instances, a lessening of the allergic state itself.

Intravenous injection of glucose at times is of special value, such as 1,000 c.c. of 5 per cent glucose by slow drip, twice daily. Aminophyllin, 0.5 to 1.0 gm. or more, may be introduced into this solution.* In some patients, 50 c.c. of 50 per cent glucose, or 200 c.c. of 10 per cent glucose, appears to exercise a therapeutic effect because of hypertonicity as well as its glucose content.

The most successful drug now available for bronchial and central nervous system relaxation when refractoriness has developed to epinephrine and aminophyllin, in our opinion, is demerol. The hazard of respiratory failure is sufficiently great to indicate the abandonment of morphine and its derivatives with most patients. At times, however, dilaudid may be resorted to if scrupulous care is given to limit the dose, such as 1 mg., by hypodermic injection two or at most four times daily for a limited period of two to four days. In 300 patients in whom we have employed demerol, no instance of physical addiction, respiratory depression, or intestinal atony has been encountered. In one of this series, psychic addiction to the drug by a patient with marked psychoneurotic tendencies became a difficult problem; in contrast to this isolated case, many patients have received remarkable benefit from its judicious administration. For patients with recurrent intractable asthma, demerol, therefore, is considered more suitable than any of the morphine derivatives.

The technique of administration is of prime importance in order to avoid side effects which initially may prejudice the patient against its use. Although the dose for an adult is 100 mg. by hypodermic or oral use, the first injection should be limited to 50 mg. since this amount is much less apt to produce dizziness, nausea, and vomiting. When a therapeutic effect is obtained with half the standard dose, it may be repeated at six to eight hour intervals, as indicated, to control paroxysms of bronchospasm. If a larger dose is required, succeeding injections may consist of 75 mg. and finally 100 mg. In the majority of patients observed in our clinic, an injection of 50 mg., followed in one hour by a second dose of 50 mg., is more apt to produce maintained bronchial and central nervous system relaxation without dizziness and nausea than a single injection of 100 mg. When the patient lies as quietly and in as recum-

*This procedure was advocated by Goodall and Unger recently (American College of Allergists, San Francisco, California, June, 1946).

bent a position as possible for two hours after administration of demerol, side effects are much less common. (The benefit derived from complete rest after administration of large doses of aminophyllin also is appreciated by the patient when it is explained to him that side effects are far less likely to take place.)

In substituting demerol for aminophyllin and epinephrine, the cooperation of the patient should be obtained by previous explanation of the purpose of the program, namely, to restore sensitiveness to drugs that he formerly relied upon, by a temporary period of relinquishing their use. Additional sedation frequently is necessary and generally is best obtained with phenobarbital in doses of 0.1 to 0.2 gm. by mouth or by hypodermic injection. After a course of five to seven days of repeated administration of demerol, iodides, and oxygen, the dose of demerol may be reduced and limited gradually to nighttime administration. For patients who respond favorably, oxygen then is stopped and potassium iodide is reduced to 0.5 c.c., two to three times daily.

For patients with more persistent bronchial spasm, the cumulative effect of repeated inhalations of 75 to 80 per cent helium with 25 to 20 per cent oxygen produces, at times, a satisfactory remission. If experienced technical supervision is available, this gas may be administered with the pressure hood under a positive pressure of 3 to 6 cm. water for periods of two to three hours, three or four times daily, for a period of four to five days. For many patients it will be found simpler to use the Meter mask with the inspiratory disc, for the inhalation of an 80 per cent helium and 20 per cent oxygen mixture, one-half to one hour, four to eight times daily.

Demand regulators, developed during the war for continuous and intermittent positive pressure which was used to combat the anoxia of high altitude flight, soon will be available for clinical use, for the administration of both helium-oxygen mixtures and 100 per cent oxygen. Positive pressure respiration with both 100 per cent oxygen and helium-oxygen mixtures reduces the pathologically elevated, negative intrapulmonary pressure during the inspiratory cycle and accomplishes a substantial relief of dyspnea and, in that way, facilitates the withdrawal of bronchodilator drugs and achievement of a satisfactory remission. These measures have been employed in a program of physiologically directed therapy of intractable asthma.[2,3,4,20,21] An injector has been added to the expiratory pressure wash which now provides inspiratory positive pressure as well; this is of great help in the treatment of asthmatic dyspnea.

Continuous nebulization of 1 c.c. of 1 per cent neosynephrine followed by 1 c.c. of 1:100 epinephrine at times is of considerable value. The combination of nebulized epinephrine and neosynephrine solutions with inhalation of a helium-oxygen mixture generally produces better bronchial relaxation than nebulizing them with pure oxygen.[28] The Meter

mask may be employed with the inspiratory disc removed, the nebulizer being attached to the oxygen inlet of the mask; the carburetor opening of the nebulizer is closed tightly with a cork after instillation of the solution. A flow of 4 to 6 liters per minute of the helium-oxygen mixture is used to nebulize the bronchodilator solutions. It may be remembered that a specified liter flow on the oxygen regulator results in a delivery 1.7 times greater than when it is attached to the helium-oxygen cylinder, since the velocity of movement of a gas through a narrow orifice is inversely proportional to the square root of the density of the gas, which is itself an illustration of its effect in clinical bronchial obstruction. An additional advantage of nebulizing bronchodilator and bronchovasoconstrictor solutions with helium and oxygen is that this gas may diffuse into areas of the lung impervious to air or oxygen alone, thus achieving more efficient alveolar ventilation and penetration of the nebulin to smaller bronchial passageways. The use of these aerosols two to four times daily frequently results in cough and the expectoration of mucoid or mucopurulent sputum.

In patients with pulmonary emphysema, the conspicuous manifestations of bronchial spasm frequently have been erroneously diagnosed as bronchial asthma. It is of considerable importance to make the distinction between uncomplicated bronchial asthma and pulmonary emphysema. In patients who are studied under the fluoroscope, the impaired movement of the flattened diaphragm is manifest in those with organic pulmonary emphysema, even in the absence of wheezing respiration. Patients with pulmonary emphysema (in the absence of an exacerbation of bronchial spasm) generally give the history of being able to assume the recumbent position without increase of dyspnea. Shortness of breath on exertion may occur in both conditions, but in patients with pulmonary emphysema, dyspnea on exertion rather than at night is characteristic, whereas in patients with asthma, nocturnal paroxysms are present almost universally. The distinction in diagnosis is of special importance in treatment.

Patients with pulmonary emphysema who are treated with complete rest in bed and demerol administered by mouth, 50 mg. three times a day and 50 mg. at bed time, frequently will manifest more or less complete freedom from the persistent bronchial spasm previously present. Hypodermic use of demerol may be employed in patients with pulmonary emphysema, but it is noteworthy that ingestion of the drug often is effective, whereas in patients with bronchial asthma, hypodermic injection generally is required. The better response of the patient with organic pulmonary emphysema to treatment with rest in bed and demerol, or rest in bed, demerol, and inhalation of oxygen, may be traced to the absence of a high pathologically elevated intrapulmonary pressure. In such a patient, intrapleural pressure approaches that of the atmosphere during both inspiration and expiration, due to loss of the elastic elements in the pulmonary parenchyma. Although refractoriness does develop to

ephedrine, aminophyllin, and nebulized epinephrine in patients with pulmonary emphysema, restoration of sensitiveness to these drugs is accomplished satisfactorily by physiologic therapy in a considerable number of patients. However, in patients with pulmonary emphysema in whom marked overinflation of the lungs is present, physiologic therapy must include longer periods of oxygen treatment with accessory measures, such as manual elevation of the diaphragm after a preliminary inhalation of nebulized epinephrine and neosynephrine. This procedure, used by Gay,* consists of placing the palms of the hands under the lower ribs and pressing them against the abdomen, inward and upward, to raise the leaves of the diaphragm during the latter third of expiration. In a certain number of patients who subsequently do not trap air quickly, ten to fifteen manual elevations of the diaphragm may result in a vital capacity of 200 to 1,000 c.c. greater than that present prior to this measure.

Miscellaneous procedures employed in intractable asthma will be referred to briefly. Anesthesia with ether at times is successful if deep relaxation is accomplished by inhalation of the gas for a period of forty minutes, or by rectal administration, such as 75 to 90 c.c. of ether mixed with an equal amount of olive oil.[16] The patient always should be attended following ether anesthesia, the head of the bed lowered, and the patient turned on his side with the face turned downward on the pillow. A pharyngeal airway, inserted after the anesthesia, may be allowed to remain in the mouth until the patient becomes conscious, when it is removed. The administration of oxygen by nasal catheter frequently is useful. Bronchoscopy under ether is often life-saving in patients past middle age, since *thorough* aspiration of mucus which cannot be expectorated may be followed by termination of the asthmatic state. The procedure seems safer and more effective when ether anesthetic is used than cocaine locally.

In patients with abundant expectoration, fever therapy generally is preferable to ether anesthesia. Good results also are obtained with fever therapy in patients with prolonged bronchial spasm and minimum expectoration.[24] Of eight patients recently treated in a hyperthermia cabinet with a temperature of 103° F. to 105° F. for three hours, four obtained a highly satisfactory remission, two were improved, and two were unchanged. Although mild or moderate attacks of asthma may recur two weeks to two months following fever therapy, the patient generally is able to control these symptoms adequately by inhalation of nebulized epinephrine or with aminophyllin by mouth.†

Although a remission may be obtained by one fever therapy, two or three additional exposures to fever at intervals of two to three days are

*Gay, Leslie: Diagnosis and Treatment of Bronchial Asthma. Baltimore: Williams and Wilkins, 1946.

†The Vaponefrin nebulizer produces particles of small size. The Vaponefrin solution which consists of a 1:75 concentration of levo and dextro-rotatory epinephrine also has been found more suitable in our experience than other varieties of 1:100 epinephrine.

more likely to result in a satisfactory remission. Artificial fever also is induced conveniently by the intravenous injection of 0.3 c.c. triple typhoid vaccine mixed with 1,000 c.c. normal saline or 5 per cent glucose, administered by slow infusion. After a chill has taken place, the infusion may be interrupted for a short period or given more slowly. When the fever is maintained for three hours, better results are obtained than when it is terminated promptly after the chill.

The use of filtered air is worthy of emphasis since new simplified window filters are available. For patients with asthma due to grass or ragweed pollen, residence in a filtered air room is apt to result in prompt relief of hay fever and bronchial spasm. The procedure also is valuable for patients who have had an excessive exposure to dust and are unusually sensitive to it. When rooms are especially equipped for filtered air, the routine precaution of having an allergen-proof cover on the pillows and the mattress should be observed. If a window filter is employed, satisfactory evidence should be available to establish its efficacy in the removal of pollen and dust. In some of the air-conditioning units used before the war inadequate filtration of pollen commonly was observed. The symptoms of hay fever and asthma will be completely relieved only if careful attention to the efficiency of the filtering agent, as well as to its actual use, is carried out. The window filter should have a leak-tight fit and the other windows and the door into the room should be kept closed. Continuous operation of the motor-blower unit is necessary to provide a steady delivery of filtered air into the room and prevent unfiltered air from entering. The removal of pollen and dust may be accomplished without electro-static precipitation.

Air filtering units, which are used commonly during the warm weather, do not provide cooling and dehumidification. However, efficiency in the filtering unit is of greater importance than cooling by an air-conditioner. Subjective comfort generally may be obtained conveniently by an additional fan to increase air movement. An efficient fan within the room combined with filtered air brought in from the outside may be found more satisfactory than the employment of a large air-conditioner, unless the latter is equipped with an unquestionably efficient device for filtration.

ANTIBIOTIC THERAPY

The treatment of infectious asthma by antibiotic therapy naturally was stimulated by the successful use of penicillin in the treatment of infection caused by Gram-positive organisms. Many reports, both favorable and unfavorable, now are in the literature concerning the efficacy of penicillin administered by injection and by inhalation as an aerosol.[11,13,14,15,17a,19,23,26] An intensive investigation has been in progress at the Presbyterian Hospital, New York City, for the past three years. The results in sixty patients with asthma have been subjected to study both from the point of view of the immediate effect as well as the follow-up

results. In our experience, the patients who were benefited markedly do not comprise a large group, although significant evidence of the therapeutic value of the drug has been observed in a number of patients. Patients who have purulent expectoration are more likely to respond to antibiotic therapy than those in whom a mucoid sputum without pus cells is present. Penicillin therapy appears to be indicated definitely for patients with an associated chronic bronchitis, bronchiectasis, or sinusitis, and in a certain number of patients in whom bronchial asthma appears in association with bronchial infection and pulmonary emphysema.

The results of penicillin treatment in terms of clinical response, duration of improvement, reactions, and effect on organisms recovered from the sputum culture are shown in Tables I and II. Many of these patients previously had been exposed to physiologic therapy with varying degrees of improvement. In this study the attempt was made to separate effects of antibiotic therapy from the additional course of physiologic treatment that could not be withheld from patients of this type. It will be observed that these patients were treated with penicillin aerosol and in some cases with systemic administration.

Of ninety-one courses of penicillin therapy in sixty patients clinical improvement was marked in sixteen patients, moderate in nineteen, slight in thirty-six, and none in twenty. Improvement attributable to physiologically directed therapy in the same series was considered marked in nine, moderate in fifty-one, and slight in nineteen. Nine patients were unimproved by either type of therapy although previously they had been benefited from physiologic therapy.

Of thirty-five patients who manifested marked or moderate improvement due to penicillin therapy, duration of improvement was over two months in twenty-one and less than two months in fourteen. Of sixty showing marked or moderate improvement due to physiologically directed therapy, improvement was sustained over two months in thirty-nine and less than two months in twenty-one.

Reactions to penicillin necessitating interruption of therapy occurred during twenty-four of the ninety-one courses. Exacerbation of asthma was seen in fifteen patients, urticaria in ten, sore, reddened tongue in seven, and fever and swollen joints in one.

In fifty-five patients from whom sputum cultures were obtained before and after penicillin therapy, forty-one showed disappearance of the original predominating Gram-positive cocci and subsequent predominance of Gram-negative bacilli.

The association of sinusitis with intractable asthma is well known and has been subjected to renewed investigation. Although extrinsic allergic factors may maintain both sinusitis and asthma in many persons, the presence of purulent secretion in the nose, with clinical and x-ray evidence of sinusitis, has appeared to be a proper indication to attempt to

TABLE I. BRONCHIAL ASTHMA TREATED WITH PENICILLIN AND PHYSIOLOGICALLY DIRECTED THERAPY

Case No.	Sex and Age	Additional Diagnosis	Course	Route of Administration* and Total Dosage	Duration of Therapy (days)	Improvement Due to Penicillin Therapy	Improvement Due to Physiologically Directed Therapy	Duration of Improvement	
								Less Than Two Months	More Than Two Months
1	M 36	Pulmonary emphysema, chronic bronchiolitis	1	I. 1,060,000	9	marked	moderate	+	
2	F 61	Pulmonary emphysema, pulmonary fibrosis	1	I. 660,000	7	marked	moderate		+
			2	I. 1,300,000 I.M. 470,000	7 14	none	slight		
			3	I. 3,400,000 I.M. 6,426,000	16 11	none	none		
3	F 40	Pulmonary emphysema, pulmonary fibrosis, chronic bronchitis	1	I. 1,400,000	7	moderate	moderate	+	
4	M 52	Pulmonary emphysema, pulmonary fibrosis, cardiac insufficiency	1	I. 840,000	7	slight	slight		
5	F 60	Pulmonary emphysema, pulmonary fibrosis	1	I. 2,500,000	8	marked	moderate	+	
			2	I. 2,000,000	10	marked	slight		+
6	M 57	Bronchiectasis, pulmonary emphysema, chronic sinusitis	1	I. 1,400,000	7	marked	marked	+	
			2	I. 2,400,000	21	none	moderate	+	
			3	I. 1,728,600 I.M. 1,030,000	19	slight	slight		
			4	I. 4,350,000 I.M. 3,180,000	35 12	slight	slight		
7	F 63	Pulmonary emphysema, chronic bronchitis, chronic sinusitis	1	I. 1,770,000 I.M. 840,000	10 7	moderate	moderate	+	
			2	I.M. 1,230,000 I.M. & S.C. 2,250,000	11 10	slight	moderate	+	
			3	O. 3,800,000	9	slight	marked	+	
			4	I. (NS) 300,000 I.M. 500,000	3 3	slight	moderate	+	
8	M 62	Bronchiectasis, pulmonary emphysema, chronic bronchitis	1	I. 1,040,000	10	moderate	moderate	+	
9	F 42	Pulmonary emphysema, chronic bronchitis, chronic sinusitis	1	I. 1,500,000	10	moderate	marked		+
			2	I. 300,000 I.M. 5,392,500	3 25	slight	moderate	+	
			3	I. 3,000,000	21	moderate	slight	+	
			4	I. (N)S) 1,000,000	10	marked	slight		+
			5	I. 2,125,000 I.M. 3,400,000	17	marked	slight		+
			6	I. 3,000,000	21	moderate	slight	+	
10	M 53	Chronic bronchitis	1	I. 1,050,000	5	marked	moderate		+
11	F 71	Pulmonary emphysema, chronic bronchitis, chronic sinusitis	1	I. 2,050,000	8	marked	moderate		+
			2	I. (NS) 6,000,000	70	moderate	moderate		+
12	M 39	Chronic sinusitis, pulmonary emphysema	1	I. 1,600,000 I.M. 800,000	8	none	none		

12	M 59	Chronic sinusitis, pulmonary emphysema	1	I. 1,600,000 I.M. 800,000	8	none	none		
			2	I. 1,000,000 I. (NS) 1,500,000	10	slight	slight		
13	F 49	Acute bronchitis	1	I. 2,100,000	5	slight	none		
14	M 49	Pulmonary emphysema	1 2	I. 2,200,000 O. 3,000,000	12 4	moderate none	moderate none	+	
15	F 50	Chronic sinusitis, chronic bronchitis	1	I. 1,520,000	9	slight	moderate		+
16	M 27	Chronic sinusitis, bronchiestasis	1	I. 8,500,000 I.M. 1,215,000	42 22	marked	moderate		+
17	M 60	Pulmonary emphysema, chronic sinusitis	1	I. 2,440,000 I.M. 370,000	14 5	none	moderate		+
18	M 33	Pulmonary emphysema, chronic sinusitis	1 2	I. (NS) 4,000,000 I. (NS) 2,100,000	20 14	marked marked	slight none	+	+
19	M 47	Pulmonary emphysema, bronchiectasis, pulmonary fibrosis, rheumatoid arthritis	1	I. 540,000 I.M. 1,155,000	5 10	none	slight		
			2	I. 3,250,000 O. 3,300,000 I.M. 7,650,000	60	none	slight		
20	M 46	Pulmonary emphysema, chronic sinusitis, chronic bronchitis	1	I. 6,766,700 S.C. & I.M. 6,760,000	33 21	slight	moderate	+	
			2	O. 11,200,000	14	none	moderate		+
21	M 67	Pulmonary emphysema, bronchiectasis	1	I. 3,000,000 I.M. & S.C. 2,800,000	15 12	slight	moderate		+
22	M 60	Bronchiectasis, pulmonary emphysema	1	I. 1,300,000 I.M. 1,000,000	7	moderate	moderate	+	
			2	I. 2,000,000	14	slight	moderate	+	
			3	I. 1,000,000 (crystalline)	10	slight	slight		
23	M 52	Chronic bronchitis	1	I. 400,000 I.M. 300,000	3	slight	marked		+
			2	I.M. 1,120,000	7	moderate	moderate		+
24	M 53	Pulmonary emphysema, chronic sinusitis	1	I. 5,560,000 I.M. 750,000	14 3	slight	moderate		+
25	M 58	Chronic bronchitis	1	I. 1,200,000 I.M. 1,125,000	7	marked	moderate		+
26	F 44	Pulmonary emphysema, allergic rhinitis	1	I. (NS) 950,000 I.M. 1,900,000	13 14	slight	moderate	+	
27	F 46	Pulmonary emphysema	1	I. 2,000,000 O. 3,550,000 I.M. 1,800,000	10 5 6	none	slight		
28	F 53	Pulmonary emphysema, acute bronchitis	1	O. 3,300,000 I.M. 1,300,000	4 10	moderate	moderate		+
29	F 41	O	1	I. 1,800,000 I.M. 500,000	8 5	slight	moderate		+

TABLE 1—CONTINUED

Case No.	Sex and Age	Additional Diagnosis	Course	Route of Administration* and Total Dosage	Duration of Therapy (days)	Improvement Due to Penicillin Therapy	Improvement Due to Physiologically Directed Therapy	Duration of Improvement	
								Less Than Two Months	More Than Two Months
30	F 63	Pulmonary emphysema, pulmonary fibrosis, chronic sinusitis, chronic bronchitis	1	I. 3,600,000 O. 1,800,000	9	slight	moderate		+
31	F	Chronic sinusitis, pulmonary emphysema	1	I. (NS) 5,400,000 O. 7,700,000	19 10	slight	moderate		+
			2	O. 3,300,000	10	slight	moderate		+
32	M 57	Chronic sinusitis	1	I. (NS) 6,100,000 I.M. 2,320,000	15	slight	moderate		+
33	F 61	Pulmonary emphysema	1	I.M. 1,750,000 O. 1,600,000	12 2	slight	marked		+
34	M 41	Pulmonary emphysema, chronic sinusitis	1	I. (NS) 1,550,000	10	none	none		
35	M 68	Pulmonary emphysema, chronic sinusitis	1	I. (NS) 2,500,000 O. 2,000,000	10	none	none		
36	F 68	Pulmonary emphysema, chronic sinusitis	1	I. (NS) 1,000,000 O. 15,150,000	12 19	none	moderate		+
37	F 54	Pulmonary emphysema, acute pharyngitis	1	O. 5,900,000	9	slight	marked		+
38	M 10	Chronic bronchitis	1	I. 1,000,000 I.M. 1,160,000	8	moderate	marked		+
39	M 36	Chronic sinusitis	1	I. (NS) 950,000 I.M. 960,000	9 8	slight	moderate		+
40	F 57	O	1	I. 2,000,000 I.M. 1,475,000	8 9	moderate	none		+
41	F 38	Chronic sinusitis, chronic bronchitis	1	I. (NS) 1,000,000 I.M. 1,120,000	7	slight	moderate	+	
			2	I. 4,500,000	30	none	none		
42	F 57	Pulmonary emphysema	1	I.M. 650,000	8	none	none		
43	M 35	Chronic sinusitis	1	I. 2,500,000 I.M. 2,250,000	10 12	slight	moderate		+
44	M 14	O	1	I. 800,000 I.M. 1,550,000	8	moderate	marked		+
45	M 44	Chronic sinusitis, chronic bronchitis	1	I. 1,700,000 I.M. 1,375,000 I. (NS) 100,000	3 6 2	moderate	marked		+

44		bronchitis		I.M. 1,375,000 I. (NS) 100,000	6 2				+
46	M 13	Chronic sinusitis	1	I. (NS) 1,850,000	8	marked	moderate		+
47	F 36	Pulmonary emphysema, chronic sinusitis, chronic bronchitis, Periarteritis nodosa	1	I. (NS) 4,000,000 O. 3,000,000 I.M. 1,500,000	23 10 12	slight	slight		
			2	I. 1,140,000 I.M. 680,000	10 5	none	none		
48	M 52	Chronic bronchitis	1	I. 1,600,000	7	slight	moderate		+
49	M 54	Pulmonary emphysema, chronic sinusitis	1	I. 650,000	4	none	slight		
50	F 5	Pulmonary emphysema, pulmonary fibrosis, chronic pneumonitis	1	I. 2,800,000	20	moderate	moderate	+	
			2	I.M. 1,600,000 I. 4,000,000	13 26	slight	moderate		+
51	F 31	Pulmonary emphysema, chronic sinusitis	1	I. (NS) 750,000	8	slight	moderate	+	
			2	I. (NS) 3,000,000 I. 1,000,000	21 10	slight	slight		
52	F 48	Chronic sinusitis, chronic bronchitis	1	I. (NS) 1,875,000	16	moderate	moderate		+
			2	I. (NS) 42,000,000	90	slight	moderate		+
53	F 62	Chronic sinusitis, pulmonary emphysema	1	I. 1,400,000 I. (NS) 2,000,000	17	slight	moderate		+
			2	I. 4,000,000	20	none	none		
54	F 53	Chronic sinusitis	1	I. (NS) 2,400,000 I.M. 200,000	14 2	none	moderate		+
55	M 57	Pulmonary emphysema, chronic bronchitis	1	I. 1,600,000 I.M. 675,000	8 3	slight	moderate		+
56	F 14	Allergic rhinitis, subacute sinusitis, acute bronchiolitis	1	I. (NS) 1,500,000	10	moderate	moderate	+	
			2	I. 1,000,000 I. (NS) 1,000,000 I.M. 2,540,000	10 17	marked	moderate		+
57	M 50	Pulmonary emphysema, chronic sinusitis, chronic bronchitis	1	I. (NS) 3,000,000	19	none	slight		
58	F 35	O	1	I. 1,400,000 I. (NS) 500,000 I.M. 600,000	10	moderate	moderate		+
59	F 55	Pulmonary emphysema	1	I. 1,000,000	8	slight	moderate		+
60	M 33	Pulmonary emphysema, chronic sinusitis, chronic bronchitis	1	I. (NS) 5,000,000	15	marked	moderate	+	

*I — Oral inhalation
I.M. — Intramuscular injection
S.C. — Subcutaneous injection
O — Oral ingestion
I (NS) — Nasal inhalation with intermittent negative pressure

TABLE II. BRONCHIAL ASTHMA TREATED WITH PENICILLIN AND PHYSIOLOGICALLY DIRECTED THERAPY

Case No.	Course	SPUTUM CULTURES		Remarks	Remarks
		Before Treatment	After Treatment		
1	1	Strep. viridans	0	Few uriticarial spots not persisting	Marked improvement previously obtained by physiologic therapy.
2	1	Pneumococcus, type 31	No pneumococcus	0	Improvement lasted 2½ months after first course. Later, benefited from sinus treatment with aerosol and negative pressure.
	2	Strep. viridans	Strep viridans	0	
	3	Strep. viridans	B. pyocyaneus	Increased cough at start of inhalations	
3	1	Pneumococcus, type 3	No pneumococcus	0	Recurrence in ten days, but good inprovement on continued therapy at home.
4	1	Hemol. Strep. Strep. viridans	Strep. viridans	0	Marked improvement previously obtained by physiologic therapy.
5	1	Gram posdiplococci	B. coli	0	Marked improvement for one year previously obtained by physiologic therapy. Later, frequent relapses.
	2	0	0	0	
	3	0	0	0	
	4	0	0	Local at sites of injections (5% glucose with adrenalin used as diluent.)	
6	1	Strep. viridans	B. pyocyaneus	0	Striking improvement in patient previously adrenalin-fast.
	2	Strep. viridans	B. pyocyaneus B. aerogenes	0	Exacerbation of asthma on sodium penicillin aerosol.
	3	B. pyocyaneus	B. pyocyaneus	0	Re-entered hospital in severe status asthmaticus.
	4	Hemol. B. pyocyaneus	Hemol. B. pyocyaneus	0	Surgical ether anesthesia finally broke status asthmaticus, but moderately severe asthma persisted thereafter.
7	1	Strep. viridans	B. coli Strep. viridans	Increased cough on sodium salt.	Chronic bronchial obstruction, bronchospasm and infection. Respiratory invalid.
	2	Friedlander's bacillus Strep. viridans B. pyocyaneus	Hemol. B. pyocyaneus	Local at sites of injection (5% glucose and adrenalin used as diluent.)	
	3	B. pyocyaneus B. coli	B. pyocyaneus	Urticaria.	
	4	Strep. viridans Staph. aureus	0	Increase in asthma.	Expired following persistent status asthmaticus less than two years after first course of therapy.
8	1	Strep. viridans	B. aerogenes	0	Decrease in all symptoms, but patient relapsed after one month.
9	1	Strep. viridans	B. coli	0	Emphysema largely functional, but severe during status asthma.
	2	Staph. aureus Yeasts	B. aerogenes	0	
	3	0	0	0	
	4	0	0	0	
	5	0	0	0	
	6	0	0	0	
10	1	0	No gram pos. organisms	0	Exacerbation of symptoms following upper respiratory infection, with good response to therapy.

			organisms		tory infection, with good response to therapy.
11	1 2	Hemol. Staph. aureus Strep. viridans	Gram neg. bacillus 0	0 0	Previous course of I.M. penicillin ineffective. Further improvement in all symptoms on treatment with negative pressure.
12	1 2	B. coli Strep. viridans	0 0	0 0	Increased cough on aerosol. Later had surgical ether anesthesia for persistent intractable asthma, with temporary improvement.
13	1	Pneumococcus Staph. albus Strep. viridans	0	0	Intercurrent acute infection subsided, but asthma unimproved.
14	1 2	Strep. viridans 0	0 0	0 Increased asthma.	Marked initial improvement with relapse later. Exacerbation of asthma.
15	1	Strep. viridans	B. aerogenes	0	Sinisutis unimproved following irrigations and antral instillations of penicillin solution.
16	1	Strep viridans Staph. aureus	B. aerogenes	0	Reddened sore throat on sodium penicillin aerosol, but no reaction to calcium salt. Asthma subsided, but sinusitis unimproved.
17	1	0	B. coli	Increased asthma, exfoliative dermatitis.	Initial marked improvement with recurrence of asthma due to penicillin or sulfonamide sensitivity.
18	1 2	Strep. viridans 0	B. aerogenes 0	0 0	Emphysema largely functional, but severe during status asthma. Marked improvement in asthma with clearing of sinusitis.
19	1 2	Strep. viridans Strep. viridans	B. aerogenes B. coli B. aerogenes	Increased cough on sodium salt. Soreness at injection sites (with adrenalin added to penicillin.)	Relieved of status asthma, but moderate asthma persisted.
20	1 2	Pneumococcus, type 19 Strep. viridans Strep. viridans B. proteus	B. aerogenes 0	Local at injection sites (5% glucose with adrenalin used as diluent.) 0	Relieved of status asthma, ambulatory, but asthma persists. Emphysema largely functional.
21	1	Strep. viridans	B. aerogenes B. coli	Local at injection sites (5% glucose with adrenalin used as diluent.)	Asthma persists, but improved.
22	1 2 3	Strep. viridans Strep. viridans Non-hemol. Strep.	B. coli B. aerogenes B. coli	Urticaria, fever, exacerbation of asthma. Sore, reddened tongue, exacerbation of asthma. Increased dyspnea and wheezing.	Asthma persists, but improved.
23	1 2	Strep. viridans 0	0 B. aerogenes	Sore, reddened tongue on calcium penicillin aerosol. Urticaria from I.M. penicillin developing one month after therapy stopped.	Aggravation of asthma following acute bronchitis. Died two months later from bronchogenic carcinoma with metastases.
24	1	Hemol. B. aerogenes Staph. albus	B. aerogenes B. coli	Urticaria and exacerbation of asthma.	Asthma persists, but improved.
25	1	Strep. viridans	0	0	Striking decrease in cough, expectoration, and wheezing. Increase in vital capacity.
26	1	Strep. viridans	B. aerogenes	Exacerbation of asthma.	Oxygen and helium inhalations combined with usual broncho-dilator drugs afforded chief relief. Breathing exercises helped moderately.
27	1	Strep. viridans	B. aerogenes	Nausea from oral penicillin.	Slight and temporary relief from bronchial relaxation. Fever therapy with triple typhoid vaccine broke status asthma; occasional attacks controlled by bronchodilator drugs.

TABLE II—CONTINUED

Case No.	Course	SPUTUM CULTURES		Remarks	Remarks
		Before Treatment	After Treatment		
28	1	Strep. viridans	Strep. veridans	Soreness at injection sites (adrenalin added to penicillin.)	Asthma less severe following control of infection.
29	1	Strep. viridans	0	0	Urticaria, most marked at injection sites.
30	1	Strep. viridans	B. aerogenes	0	Chief benefit was from physiologic therapy.
31	1	Pneumococcus type 19	B. coli	0	Sinusitis unimproved by x-ray, although symptomatically improved.
	2	Hemol. B. coli	Hemol. B. coli	0	Asthma remained improved for one year.
32	1	Non-hemol. Strep.	B. aerogenes B. coli	Penicillin reaction manifested by increased cough, severe asthma, fever to 105°, urticaria swollen tender joints.	Asthma markedly improved following fever.
33	1	Strep. viridans	Strep. viridans	Nausea from oral penicillin. Local reaction of soreness, redness, and vesicle formation at injection sites.	Sustained improvement from physiologic therapy, including heilum.
34	1	Strep. viridans	B. coli	Increased wheezing following inhalations.	Symptoms controlled on penicillin but returned when therapy stopped. Previously responded well to physiological therapy.
35	1	Strep. viridans Hemol. Strep.	B. aerogenes	Increased wheezing following inhalations.	Some control of infection but no improvement in asthma.
36	1	B. alkaligenes	0	Sore, reddened tongue.	Intractable asthma responded to physiologic therapy despite no improvement in sinusitis on penicillin therapy.
37	1	Strep. viridans	B. aerogenes	0	Intractable asthma responded for several months to filtered air prior to use of penicillin. No bronchodilator drugs required after fifth day.
38	1	Hemol. Staph. aureus	0	0	Rapid improvement with subsidence of all symptoms.
39	1	0	0	0	Onset of asthma following intranasal surgery. Had become adrenalin-fast.
40	1	Strep. viridans	B. coli	0	Moderate asthma for eight months subsided on penicillin therapy alone without any physiologic therapy.
41	1	Hemol. Staph. aureus	B. coli	Sore, reddened tongue on aerosol; urticaria, exacerbation of asthma on combined penicillin therapy.	Improvement only temporary.
	2	0	0	0	No reaction to aerosol alone. Expired in severe status asthma one month later.
42	1	0	0	Urticaria, soreness at injection sites (adrenalin added to penicillin)	Intractable asthma failed to respond to usual physiologic therapy, filtered air, and ether anesthesia. Finally improved.
43	1	0	0	0	Previous course of I.M. penicillin without benefit. Chief improvement followed physiologic measures, including helium.

44	1	Strep. viridans	0	0	Rapid and sustained improvement.
45	1	0	B. aerogenes	0	Repeated sinus surgery and irrigations in past with improvement in sinusitis but no relief of asthma.
46	1	0	0	0	Rapid and sustained improvement.
47	1	Hemol. B. pyocyaneus	B. aerogenes B. coli	Exacerbation of asthma.	Intractable asthma for three years. Temporary improvement in hospital following fever with bronchol pneumonia. Autopsy diagnosis: Periarteritis nodosa.
	2	Hemol. B. pyocyaneus	B. aerogenes		
48	1	Strep. viridans	H. influenzae Non-hemol. Strep.	Unticaria	
49	1	Hemol. Strep.	B. aerogenes	Urticaria, exacerbation of asthma.	Previously markedly improved for three months following I.M. penicillin. Helped mainly by physiologic therapy at present.
50	1	Hemol. Staph. aureus	0	0	Clinical improvement without change in x-rays. Chief benefit from physiologic therapy although penicillin useful in controlling acute infection (organism moderately resistant to penicillin.)
	2	Hemol. Staph. aureus	H. influenzae	0	
51	1	0	B. aerogenes Staph. aureus	0	Chief benefit from physiologic therapy. Sinusitis unimproved. Only temporary improvement, chiefly from physiologic therapy.
	2	0	B. aerogenes	0	
52	1	Strep. viridans	Strep. viridans B. aerogenes	Transient pruritis.	Greater improvement in asthma than sinusitis.
	2	Strep. viridans	B. coli	Increased asthma	Asthma temporarily aggravated by calcium penicillin aerosol, and also by 15% sodium sulfacetamide aerosol. Inhalations resumed later without reaction.
53	1	Strep. viridans	Hemol. B. coli	Sore reddened tongue on calcium penicillin aerosol, and increased cough.	Intractable asthma with final refractoriness to all measures. Patient expired.
	2	0	B. aerogenes	No sore tongue using crystalline sodium penicillin aerosol.	
54	1	D. pneumoniae Staph. aureus	B. coli	0	Greatest improvement from artificial fever therapy.
55	1	0	B. coli B. aerogenes	Sore, reddened tongue and throat, increased cough.	Dyspnea and cough provoked by penicillin inhalations. Moderate relief from physiologic therapy.
56	1	Hemolytic Strep.	M. catarrhalis	0	Penicillin therapy controlled infection. Asthma improved on combined therapy. No relapse in five months.
	2	D. pneumoniae Staph aureus	B. coli	0	
57	1	0	B. aerogenes	Increased asthma	Dyspnae and bronchospasm became worse on penicillin inhalations, with slight relief from physiologic therapy.
58	1	Strep. viridans	0	0	Marked improvement following artificial fever therapy.
59	1	Strep. viridans	B. coli Hemol. Strep.	Sore, reddened tongue.	Previously had marked improvement with physiologic therapy alone.
60	1	Pneumococcus, type 17 Staph. aureus	B. coli B. aerogenes	Coated brown tongue.	Striking improvement during hospital stay and for few weeks at home. Relapse not helped by occasional inhalations in clinic.

eliminate infection in the paranasal cavities. Although surgical therapy of chronic sinusitis often has been disappointing in accomplishing a recovery from intractable asthma, the relation between infection in the sinuses and the maintenance of an asthmatic state has been confirmed by our studies, in which penicillin aerosol has been used in conjunction with negative pressure in the treatment of sinusitis.

This method of treatment, which has been recently simplified, has been of sufficient value in the eradication of acute, subacute, and chronic sinusitis to justify our recommendation for a widespread trial.[6,7,9] In some patients with intractable asthma, previously treated by oral inhalation of penicillin aerosol without significant benefit, nasal inhalation of penicillin aerosol with repeated negative pressure produced in the antra and other sinuses has been followed by a satisfactory remission of the asthmatic state, coincident with clearing of infection in the sinuses. Four inhalations of 50,000 units of penicillin nebulized by a flow of 6 liters per minute of oxygen are employed generally each twenty-four hours, for a period of ten to twelve days or more. The negative pressure is produced by a flow of oxygen through a venturi tube; when the horizontal arm is connected by suitable tubing to the nose, a negative pressure of 50 mm. Hg has been demonstrated in the antra. When the flow of oxygen is directed through the vertical end of the venturi, penicillin is nebulized and blown into the nasal passages. Intermittent termination of negative pressure in the sinuses is followed by the introduction of a relatively dense mist of penicillin and lodging of the drug on the mucous membrane, as revealed by washings from the antrum following inhalations by this method.

The efficacy of penicillin therapy in bronchial and sinus infections depends on (1) the presence of penicillin-sensitive organisms as etiological factors, and (2) the establishment of a therapeutically active, local concentration of the drug. Following penicillin therapy, Gram-positive organisms disappear from the bronchial and nasal secretions and consistently are replaced by the Gram-negative organisms, B. coli and coliform bacteria, B. pyocyaneus, B. aerogenes, and B. proteus. To what extent these organisms were present prior to treatment is difficult to determine, but in more recent studies the search for Gram-negative organisms before treatment has been regarded frequently by isolating them in small numbers. After three to ten days of treatment, these Gram-negative organisms grow in either pure or predominating culture. A favorable therapeutic result may take place in some patients, irrespective of the presence of Gram-negative bacteria. If purulent secretions continue, the failure of clinical improvement appears to be related to the presence of these Gram-negative organisms. As pointed out by Abraham and Chain,[1] Foster,[12] and Meleney,[17] an enzyme produced by Gram-negative bacteria, "penicillinase," may inhibit the bacteriostatic effectiveness of penicillin. In a few instances the colon bacillus may exert a pathogenic action in itself. The use of strep-

tomycin aerosol in combination with penicillin in some patients will result in a successful therapeutic response when penicillin alone has been followed by no alteration in the symptoms. This sequence of events has been demonstrated especially in patients with bronchiectasis, reported by Olsen.[18] In many patients with bronchopulmonary infection, including bronchitis, bronchiectasis, and lung abscess, marked clinical improvement has been observed, even with the persistence in the sputum culture of Gram-negative organisms following treatment.[10,22,23] Other agents, such as 5 per cent sodium sulfathiazole with 5 per cent sodium sulfadiazine, are being investigated as agents to control the growth of Gram-negative organisms when combined as aerosols with penicillin.

Two complications of aerosol therapy need comment. The development of urticaria, which occurs more frequently after penicillin treatment in allergic persons, nevertheless is less common in aerosol sinusitis treatment than in systemic administration. When it does occur, the employment of pyribenzamine is apt to be followed by a satisfactory control of symptoms. The drug may be required in 100 mg. doses four times a day for two to five days, but it is remarkably effective and prompt in the termination of urticaria in the majority of patients. In some instances ephedrine may be employed in combination. The treatment of the patient temporarily is interrupted; when it is thought desirable to continue therapy, a different brand of penicillin or the substitution of crystalline penicillin may permit a second course without development of urticaria. In a few patients in whom severe allergic reactions have occurred, with pains and swelling of the joints, penicillin treatment has been stopped permanently.

The second complication that may occur as the result of aerosol therapy is a reddening or blackening of the tongue. This has been noted previously with the administration of penicillin dissolved in water or in Amphojel and water, even though the concentration of the drug has been under 500 units per cubic centimeter.[5] The tongue and, at times, the throat become not only reddened but sore. In sinusitis treatment, in which nasal inhalation takes place, the occurrence of either a red or black tongue is rare, provided a small hole about ¼ inch is made in the rubber bag, now rarely used; penicillin mist may be delivered to the outside air rather than exhaled through the mouth. In oral inhalation of penicillin the symptoms of tongue irritation are more common. If the mouth is rinsed with water before and during each inhalation and if the throat is sprayed with water from an atomizer before and during the inhalation, the large penicillin particles are dissolved on the moist pharyngeal surface and the complication appears to be less frequent. At times, treatment must be interrupted for two or three days until the tongue resumes its normal color. Just what the mechanism of either blackening or reddening of the tongue is based on has not been determined. In some patients, penicillin aerosol may be inhaled for a period of one year without any noticeable effects on the

tongue; in others it becomes red within two or three days. Some physicians have placed white vaseline on the tongue prior to treatment as a method or avoiding this complication. Tartar on the teeth at times has been observed to be diminished after a course of penicillin aerosol therapy.

Although we have employed 50,000 units of penicillin per cubic centimeter of normal saline or distilled water, using the calcium salt or preferably crystalline penicillin, lower concentrations may be used. If the nebulizer is attached to a Meter mask with the inspiratory disc removed, the patient may breathe penicillin aerosol with oxygen in a mask over longer periods of time at concentrations of 10,000 to 20,000 units per cubic centimeter. Another comfortable method recently used is a hood tent which encloses the head and makes closure at the neck. It is similar to the open top tent, except that the roof of the hood is closed over.

With the glass mouthpiece aerosol rebreathing apparatus,[8] blood levels of 0.1 to 0.2 units per cubic centimeter of serum generally are obtained for two hours after the inhalation of 50,000 units of penicillin aerosol. With mask or hood-tent administration, effective blood levels have been found with higher doses, such as 100,000 units per cubic centimeter. In the treatment of pneumococcus lobar pneumonia, lower blood levels are effective, therapeutically, such as 0.03 units per cubic centimeter, obtained after inhalation of 25,000 units per cubic centimeter at two-hour intervals.[22] The administration of penicillin by intramuscular injection has been shown to result in the cure of pneumonia in some patients when administered for a period of twelve to sixteen hours during the day.[25] The maintenance of a therapeutic blood level during the day by five inhalations of penicillin aerosol and, in addition, the local deposition of penicillin particles add to the efficacy of treatment in those patients in whom bacteria grow on a purulent or fibro-purulent membrane not reached by a capillary blood supply. In some instances, a retiring dose of penicillin has been given either by mouth or intramuscular injection.

In many patients a course of twelve days to two weeks has been used in the treatment of bronchial asthma, with a daily dose of 250,000 units administered as an aerosol; the precise indication for length of treatment is determined by the clinical condition of the individual patient.* In patients with bronchiectasis, penicillin therapy occasionally has been maintained for a period of a year. The nature of the infection, the penicillin sensitivity of the predominating organism determined by culture of the sputum, the presence or absence of Gram-positive organisms, and many other factors must be taken into consideration before appraising the indications and duration of antibiotic therapy.

The frequency of recurrence of asthmatic symptoms in patients who responded favorably to antibiotic therapy led to the subsequent use of weekly injections of catarrhal vaccine and dust. It has been our impres-

*Intramuscular injection of the drug is now preferred to avoid the wheezing which may be caused by inhalation of penicillin mists, unless highly resistant organisms are present.

sion that patients, to whom follow-up treatment was given with the standard procedures employed in desensitization with dust and stock vaccine, have fared much better, in terms of maintained improvement, than patients to whom a single or several courses of penicillin have been given without attempts to increase the immunologic and allergic resistance of the patient. Furthermore, this hyposensitization program also would seem to be of value for patients with bronchial asthma who have been treated for sinus infection.

SUMMARY

A report is presented on the effectiveness of physiologic and antibiotic therapy in severe or intractable bronchial asthma.

In patients who develop refractoriness to epinephrine and aminophyllin, temporary curtailment of the use of these bronchodilator drugs and substitution of other measures are required to obtain a remission from intractable asthma. The effective administration of demerol, generally in conjunction with continuous inhalation of 50 per cent oxygen, is the simplest program to terminate a state of persistent bronchial spasm. Intravenous injection of isotonic or hypertonic glucose often is a helpful adjunct. Physiologic therapy also includes helium-oxygen inhalations, positive pressure respiration, ether anesthesia, bronchoscopy, and artificial fever therapy for patients who do not respond to simpler measures.

Antibiotic therapy for bronchial asthma by administration of penicillin, either intramuscularly or by aerosol, has a limited although unquestionable value in selected cases. The repeated introduction of penicillin aerosol into the paranasal sinuses, following the release of a previously established partial vacuum, has been followed by clinical recovery in acute, subacute, and chronic sinusitis and, in some instances, with clearance of the symptoms of intractable asthma.

Of ninety-one courses of penicillin therapy in sixty patients with severe bronchial asthma, clinical improvement was marked in sixteen, moderate in nineteen, slight in thirty-six, and absent in twenty. The duration of improvement in thirty-five patients who were moderately or markedly benefited was over two months in twenty-one and less than two months in fourteen. In sixty patients who manifested marked or moderate improvement as a result of physiologic therapy, improvement was sustained over two months in thirty-nine and less than two months in twenty-one.

More sustained improvement after antibiotic penicillin therapy in the treatment of bronchial and sinus infection appears to take place in patients in whom hyposensitization therapy with catarrhal vaccine and dust is instituted directly after treatment and continued for an indefinite period.

Further studies are required to determine the role of Gram-negative organisms which appear subsequent to penicillin therapy in cases of bronchopulmonary and sinus infections. Current investigations of strep-

tomycin and sulfadiazine and sulfathiazole aerosols point to the possibility that patients with mixed infection unresponsive to penicillin therapy may be benefited by antibiotic treatment effective against both Gram-positive and Gram-negative bacteria.

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(Continued on Page 352)

MANAGEMENT OF BRONCHIAL ASTHMA

The Use of 1-(3,' 4'-Dihydroxyphenyl)-2-isoproprylaminoethanol

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IT is the purpose of this report to enlarge upon our original observations[16] regarding a new sympathomimetic amine,* (1-(3', 4'-Dihydroxyphenyl)-2-isopropylaminoethanol, $(HO)_2C_6H_3CHOHCH_2NHCH\ (CH_3)_2$, which appears to be particularly effective in relieving the dyspnea of an asthmatic attack. Sympathetic amines elicit body responses which simulate those resulting from stimulation of adrenergic nerves, but the location and intensities of these responses differ widely. As far as we know, these are the first reports on this effective pneumodilator in this country.

During the war years, sparse reports from Europe[8,9,10] on the use of this drug, known there as "Aleudrin," became available. It was effective in the control of asthma when used as a simple spray and it furthermore quickly stopped the experimental dyspnea crises induced in healthy subjects by choline aerosols. Experimental work also indicated[11,15,22] that the relaxing action of this drug on bronchial spasm, induced by pilocarpine, was ten times greater than that of epinephrine. Although the drug does not fundamentally alter the basic physio-pathologic condition of bronchial asthma, it is a valuable adjunct in the armamentarium of therapy for this distressing condition.

TECHNIQUE EMPLOYED

The value of the inhalation of therapeutic aerosols can be appreciated if one recalls the tremendous absorptive powers of the inner surface of the lung whereby an inhaled medicament almost immediately reaches the desired objective and is not partially dissipated in a circuitous circulation which itself may not be functioning properly. With these aerosols it is possible to obtain high local concentrations and varying blood levels. During the past few years this therapy has gained impetus from the many new drugs which have become available, notably penicillin aerosol with its proven efficacy in conditions formerly resistant to medical treatment.[1,2,3,7,17,18]

The effects of 187 inhalations of Isuprel in eighty-two ambulatory patients with chronic bronchial asthma were studied. Forty hospital patients with severe bronchial asthma were treated and more than half have been followed for varying periods after discharge from the hospital. In the latter group the subcutaneous and oral routes were also employed but the inhalatory route was used far more than the others. The vaponefrin[14]

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*Isuprel—This work was aided by a grant from Frederick Stearns & Company.

nebulizer* was used in all cases and a length of rubber tubing connected it with a regulator attached to an oxygen tank. Oxygen flows of four to five liters were usually sufficient to aerosolize 1.0 c.c. of the Isuprel solution in ten minutes. The subcutaneous route, with solutions of 1:1000, 1:5000 or 1:10,000, was generally used only to initiate the treatment of the acute attack. When the acute attack had been successfully combated, the inhalatory route, alone or in conjunction with the oral, proved adequate. Some of the earlier patients were treated with amounts later shown to be inadequate. Had they been treated with the later established optimum doses their improvement would have been much greater. Also, since the preliminary report, the 1:100 dilution has not been available for nebulization in the follow-up of discharged patients or the treatment of new admissions. A solution of one-half this strength has been used, which has not been as effective. In general, 1.0 c.c. of 1:100 dilution by the inhalatory, 0.2 to 0.3 c.c. of the 1:1000 dilutions by the subcutaneous, and 5 to 10 mg. by the oral route, every three to six hours, gave the best results.

The term "bronchospasm" is used to denote that narrowing of the bronchi and bronchioles which leads to the difficulty in breathing manifested by typical wheezes, squeaks and rhonchi, and by prolonged expiration. This is graded 1+, 2+, 3+ and 4+ and is purely a subjective classification based on the intensity of these sounds from barely audible to extremely loud, the last (4+) being the type heard in the most acute attack.

Vital capacity readings were taken on the McKesson Scott vital capacity apparatus which is convenient because of its easy portability. Many factors enter into any one vital capacity reading which may render it erroneous; e.g., familiarity of the patient with the procedure, age, cough, exhaustion, lack of co-operation, state of dentition, emotions and fear during an attack. However, while certain individual readings may be incorrect when the above factors are involved, it is felt they usually serve as a criteria of a drug's effectiveness and are extremely valuable if taken frequently during a hospitalization period of several days. Widely separated vital capacity readings are very apt to be incorrect, but in most cases the readings taken immediately before and after administration of a drug offer an objective comparison of its effectiveness.

AMBULATORY PATIENTS

Thirty-nine of these patients were intrinsic asthmatics, twenty-nine extrinsic, thirteen were mixed; four had hay fever and four had chronic bronchitis and bronchiectasis concomitantly. There were forty-two males and forty females, the average age being forty-five years, and ranging from eight to seventy-two years.

Figure 1 illustrates the vital capacity changes for 187 trials in eighty-

*Obtainable from Vaponefrin Company, Upper Darby, Pennsylvania.

two patients with varying degrees of bronchospasm, employing inhalations of 0.25 to 1.5 c.c. of 1:100 or 1:200 dilutions of isuprel.

As would be expected, the greater the bronchospasm the less the pre-

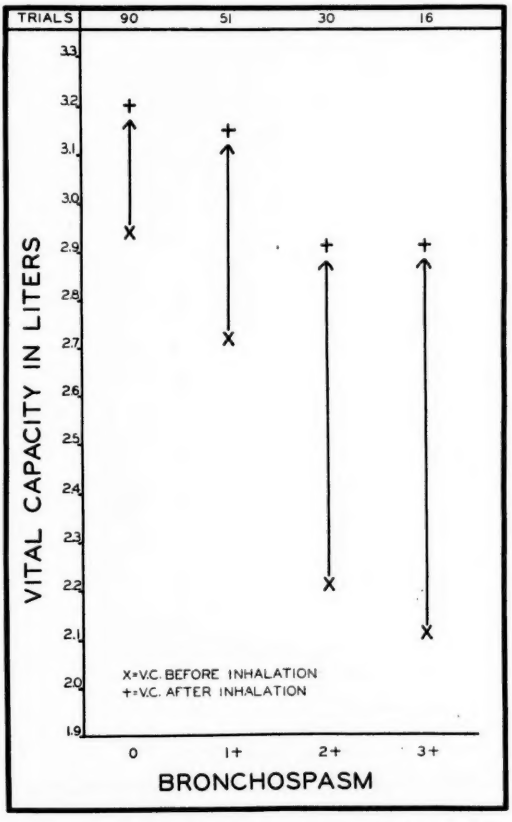

Fig. 1. Averages of 187 vital capacity recordings on eighty-two ambulatory patients, with various degrees of bronchospasm using various dilutions (0.25 c.c.-1.5 c.c. of 1:200 and 1:100) of isuprel by oxygen-aerosolization.

treatment vital capacity reading. The average vital capacity of ninety trials in asthmatic patients (Figure 1) without wheezing or rhonchi or prolonged expiration was 2.94 liters, while that of sixteen trials in patients with 3+to 4+ spasm was only 2.11 liters. The vital capacities in patients with 1+ and 2+ bronchospasm were at proportionate levels. Figure 1 also illustrates that the greater the bronchospasm present, the greater the increase in the vital capaciy immediately following a treatment. When no bronchospasm was present, the average increase was only 0.26

liters as compared to 0.43 liters, 0.70 liters, and 0.80 liters, respectively, as the bronchospasm becomes greater.

Figure 2 illustrates the same changes for 134 trials in seventy-four

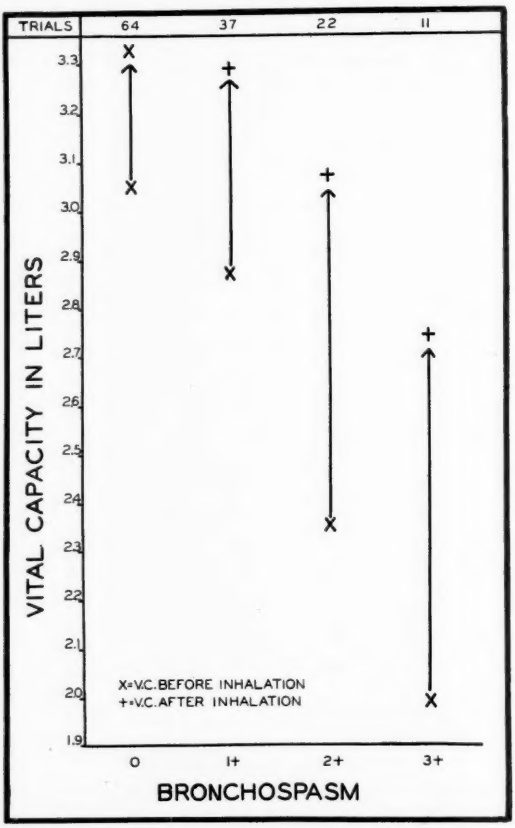

Fig. 2. Averages of 134 vital capacity recordings on seventy-four ambulatory patients with various degrees of bronchospasm using 1.0 c.c., 1:100 isuprel by oxygen-aerosolization.

patients when inhalations of 1.0 c.c. of 1:100 dilutions alone were used.

Figure 3 shows the gratifying response to the drug when the distressing asthmatic cough was present although no physical signs of bronchial obstruction were found. The sixty-four trials shown in Figure 2, where signs of bronchospasm were absent, were done in forty patients. During thirty-seven of these trials, cough was absent; in twenty-seven, the typical, hacking asthmatic cough was present. All were treated by oxygen-aerosolization with 1.0 c.c. of 1:100 isuprel. In those with cough an increase of 0.50 liters was noted, while the other group showed a negligible increase of 0.19 liters. This was particularly surprising since a

persistent cough often results in a poor vital capacity reading. The fact that the pretreatment reading was so low was therefore to be expected, but the swift allaying of the cough which followed inhalation, thereby increas-

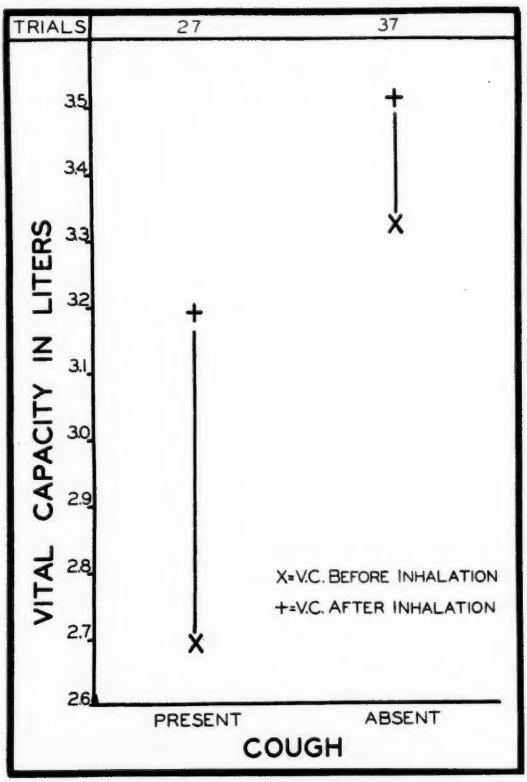

Fig. 3. Averages of sixty-four vital capacity recordings on forty ambulatory patients without signs of bronchospasm using 1.0 c.c., 1:100 isuprel by oxygen-aerosolization, illustrating the effect on asthmatic cough.

ing the vital capacity of these subjects to almost the same level as those without cough, is indeed striking. In addition, several of the ambulatory and hospital patients volunteered the information that expectoration was easier and greater immediately following each inhalation.

HOSPITAL-TREATED CASES

Forty hospital patients were treated with this drug alone. Most asthmatics who deserve hospitalization are generally real problems in therapy and the most intensive programs of repeated bronchiolar relaxation[4,5,19,20,21] are necessary to keep them controlled. Such programs require the judicious use of various medicaments, e.g., infusions of glucose, saline or

typhoid, aminophyllin, epinephrine, rectal ether or paraldehyde, positive pressure oxygen or helium-oxygen mixtures and other methods in the first thirty-six to seventy-two hours. However, adequate evaluation of a new drug requires its use alone. Under such circumstances any success may be multiplied somewhat when it is considered how much more valuable the drug will be when used in conjunction with other tried and proved medicaments.

The general program of treatment consisted of 1.0 c.c. of 1:100 dilution every three hours by the oxygen-aerosol technique, omitting one or more night doses, if possible, to allow uninterrupted sleep. The first nine patients were carried on smaller doses than this; nevertheless, all will be considered as a group. Three patients did not receive any inhalation but were treated by oral and subcutaneous routes. One of these was listed as an equivocal result, another as slightly improved, and the third as a failure. Unavoidable factors which at times contributed to irregularity of treatment included an acute shortage of nurses and temporary lack of the drug due to manufacturing difficulties.

The forty hospital patients had a total of fifty-five admissions. A great many were in the severest stage of status asthmaticus when first seen, most having run the gamut of therapy without success before isuprel was tried. Of these, thirty-five were intrinsic, one extrinsic and four were mixed asthmatics. There were seventeen males and twenty-three females, the average age being forty-one years and ranging from thirteen to sixty-nine years. The average duration of asthma was thirteen years, ranging from two to fifty years.

Of the total admissions, eight patients had two admissions, two had three, and one had four. Four of the readmissions were extremely brief and, since they were not treated with isuprel, will be disregarded in the tabulation of results.

Twenty-seven patients during thirty-seven admissions were quickly and markedly improved, seven in as many admissions were moderately improved, three in as many admissions were slightly improved; in one the results were equivocal and two patients with three admissions were classified as failures.

In other words, 85 per cent of the severely ill hospital-treated patients were kept comfortable by this drug alone. In terms of treated admissions, 80 per cent were successful. Since, with one exception, all the cases were either the intrinsic or mixed type of asthma, a notoriously treatment-resistant group, such a proportion of success is most gratifying. In no case did we note resistance to the drug comparable to the epinephrine-fast stage. Of the failures, one (C.J., Case 35) received only two 0.5 c.c. injections of the 1:5,000 dilution subcutaneously among the multiple treatment measures that were employed. All measures failed and she died within forty-eight hours after admission. The other patient who was classed as a failure (L.P., Case 24) was desperately ill during each

of two admissions. During the first he failed to react very dramatically to either the subcutaneous or the inhalatory route. During his second admission bronchoscopy proved to be the life-saving measure. Every two hours for more than forty-eight hours during the critical period of this admission, 0.5 c.c. of the 1:5,000 dilution was injected subcutaneously. This treatment was apparently of benefit, but too many other measures were used concomitantly for accurate evaluation. He was later carried along on nebulization alone and for several months since discharge has done exceedingly well with the use of the hand-bulb nebulizer. Nevertheless, he is classified as a failure.

The three patients classified as "slightly improved" had minimal bronchospasm to begin with and there was not much room for improvement. One has had an excellent course since discharge with no time lost from work as compared with many incapacitating periods and frequent hospital admissions before the inception of this drug. The one "equivocal" result was obtained in a highly neurotic and agitated female. Excellent objective improvement, as manifested by disappearance of cyanosis and quieting of the accessory muscles of respiration, followed 0.33 c.c. subcutaneous injections of the 1:1,000 dilution. However, she would not quiet down until a nasal catheter was inserted, although, unknown to her, the oxygen flow was not turned on. Of the readmissions three were for failure of oral therapy, one was for failure of 1:100 and four were for failure of 1:200 dilution isuprel sprays with hand-bulb nebulizer to control severe attacks. Three occurred in patients who either ran out of isuprel or were not taking it while at home.

FOLLOW-UP CARE

Twenty-four patients have been treated following discharge. Due to a limited supply of the drug only the patients with a history of chronic perennial asthma were treated. The likelihood of remission in such cases was minimal and therefore more adequate evaluation of ambulatory management was possible. Five have been followed for less than two months and will not be considered. Several have been treated for six months which is the longest follow-up period. Considering the vagaries of the average asthmatic no definite conclusion can be drawn on the basis of such a short follow-up period. However, definitely favorable trends have been noted.

About half of these patients are employed. All have lost much less time from work than on previous routines of management. It is impossible to estimate this advantage in total dollars and cents but it must be considerable. One patient has been in a sanatorium for six months and has done very well. Only three patients—extremely severe asthmatics with a total of eight hospital admissions—have failed to attain a successful ambulatory regime with isuprel. Two of them, nevertheless, insist that isuprel is more effective than anything they have used.

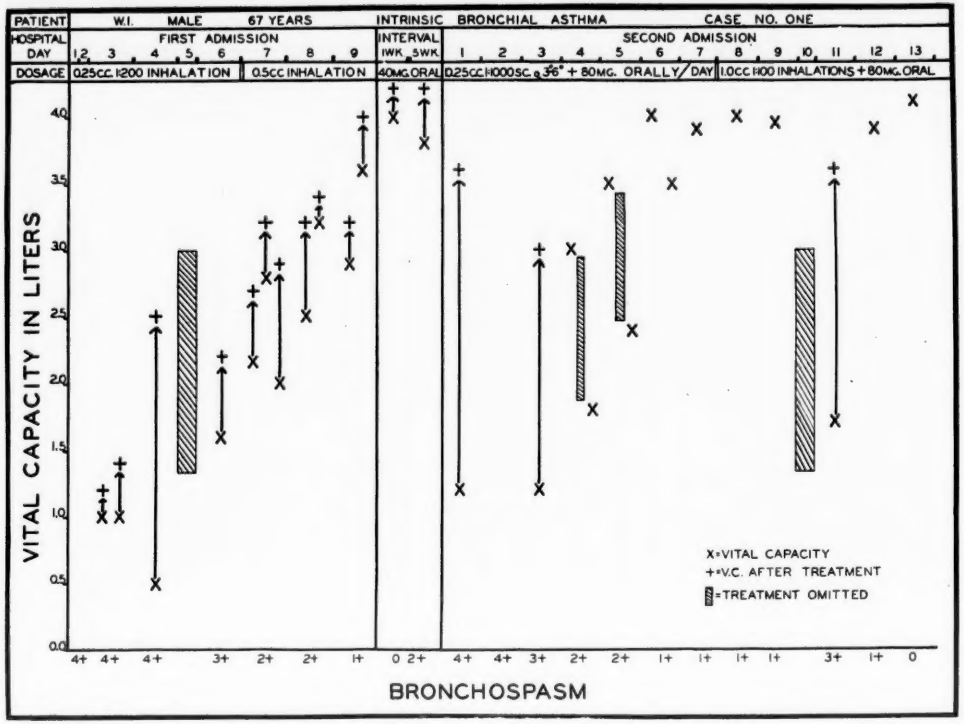

Fig. 4. Vital capacity recordings during two hospital courses (Case 1) treated with isuprel by various routes.

Therefore, 84 per cent of the chronic severe group, which has been followed after discharge from the hospital, have had successful ambulatory courses. Many of the patients had to be changed from the 1:100 to 1:200 solution for hand-bulb nebulization when the former dilution became unavailable. They have noted less effectiveness with the latter, having had to use larger amounts at shorter intervals for adequate control. Brief abstracts of some of the hospitalized cases follow.

CASE REPORTS

Case 1.—W. I., aged sixty-seven, male, with severe intrinsic bronchial asthma for two years, had been extensively studied and treated allergically with equivocal results. He entered the hospital in status asthmaticus and was given oxygen-aerosol treatment with 0.25 c.c. of 1:200 isuprel (Fig. 4). Though inadequate, this dosage did lead to improvement but it had to be reinforced with other treatment during the first thirty-six hours. After that he showed a regular daily rise in vital capacity readings. Following discharge from the hospital, he took approximately 40 mg. a day orally in divided dosages and maintained a vital capacity of over 4 liters for two months until another severe attack necessitated readmission. During his second admission, he was treated with larger doses from the start and had a smoother course, consistently maintaining a vital capacity above three liters except on three occasions during his thirteen-day stay when isuprel was either temporarily unavailable or inadvertently omitted. The first seven days of his second admission he was also tried on a regime of subcutaneous injections every three to six hours and 10 mg. orally every three hours. This did not control him as well as the oxygen-aerosol technique employed during the last six days, since the effects of the subcutaneous route wore off too quickly. He has been able to return to his work as a janitor, using handbulb sprays of 1:100 isuprel several times daily and 10 mg. orally four times a day. His vital capacity has been maintained at 4 liters for several months since his discharge.

Case 4.—B. M., aged twenty-one, female, with a history of chronic asthma for fourteen years and severe asthma for three days, entered the hospital in an epinephrine-fast state. Concomitant nausea, vomiting and unexplained diarrhea contributed to a highly distraught and weakened condition. She had dramatic relief from 0.5 c.c. of 1:1,000 subcutaneous isuprel. Figure 5 shows her subsequent improvement with oxygen-aerosolization of 1.0 c.c. of 1:200 isuprel. When asked to compare this mode of treatment with past routines on previous admissions, she answered enthusiastically that isuprel "worked atomically."

Case 5.—A. H., aged eighteen, female, with bronchial asthma for seventeen years, who had been in the hospital more than thirty-six hours without relief in spite of intensive therapy, showed excellent response to 0.5 c.c. of 1:1,000 isuprel subcutaneously. Maintained thereafter on inhalations of 1.0 c.c. of 1:200 dilutions every three hours, she had a progressively good hospital course. She was readmitted briefly a week later because the oral isuprel alone failed to control her. Since discharge she has done exceedingly well by using hand-bulb inhalations once or twice a day, finding them particularly effective during the past six months in aborting all attacks.

Case 6.—E. M., aged twenty-six, female, with bronchial asthma for eighteen years, was treated under circumstances almost identical to Case 5 and her hospital course, shown in Figure 5, illustrates both cases for all practical purposes. She, too, had been in the hospital for many hours without relief despite varied treatment, but

responded immediately to 0.5 c.c. of 1:1,000 subcutaneous isuprel. When technical difficulties obviated oxygen-aerosol during the night, she required another injection to the following morning. Thereafter she showed continued progressive improvement. Both these patients (Cases 5 and 6), with a total of five previous hospital admissions, found isuprel far more effective than previous routines of therapy.

Case 7.—G. C., aged fifty-three, male, with bronchial asthma of fifteen years' duration, was seen twenty hours following admission. In spite of intensive therapy, including infusions of saline, or dextrose and saline with aminophyllin, epinephrine subcutaneously, aminophyllin by rectum and luminal, his condition appeared progressively worse. Figure 6 illustrates the immediate excellent vital capacity response to 0.75 c.c. of 1:1,000 subcutaneously and the subsequent improvement on 1.0 c.c. of 1:200 inhalations. *In this patient and in several others the inhalation was repeated immediately, and in this dilution a cumulative effect on the vital capacity recordings was noted.* When ready for discharge, however, he developed a vesicular eruption with crusting around the lips and inhalations were discontinued. Seven hours later he developed another asthmatic attack which resisted epinephrine and aminophyllin injections for thirty-six hours. He was placed on 15 mg. isuprel orally every three hours and showed a gradual improvement during that day. After a few days, some nervousness occurred with this dosage and the dose was subsequently reduced to 10 mg. every three hours. Except for two periods where the drug was inadvertently skipped for nine hours, he manifested progressive improvement as shown by his vital capacity readings.

Case 11.—L. M., aged thirty-one, female, entered in extreme status asthmaticus. She had been quite dyspneic for one week but obtained partial relief from aminophyllin intravenously. She accidentally received 20 grains of aspirin at this time and shortly thereafter her attacks became extremely severe. Two years ago she had a similar experience following the use of aspirin and was in status asthmaticus for four days. She was given 20 c.c. aminophyllin intravenously and 0.5 c.c. epinephrine subcutaneously with no response. One-half hour later she was given 30 c.c. of ether in 60 c.c. of oil rectally, and this was repeated in one hour. She continued dyspneic, wheezing and cyanotic and received 1,500 c.c. of 5 per cent glucose in saline with aminophyllin. Four hours following entry there was no appreciable change from the admission picture except a more profound picture of exhaustion. She was given 1.0 c.c. of 1:200 isuprel by inhalation and within a few minutes responded dramatically, breathing much easier. Approximately six hours later she experienced another severe attack which also responded quickly to 0.5 c.c. 1:1,000 subcutaneously. Thereafter, except for marked weakness for twenty-four hours, she improved progressively, with 1.0 c.c. 1:200 every three hours by oxygen-aerosolization. On the fifth hospital day, upon learning that her x-ray showed bilateral tuberculosis, she left the hospital. She was readmitted eleven days later in a moderate attack and this responded quickly to oxygen-aerosolization of isuprel. She spent three and one-half uneventful weeks while awaiting sanatorium accommodations. During this period, and since that time while in the sanatorium, she has been relatively free of acute attacks and more comfortable than she has been in years by the daily use of nebulized isuprel and approximately 60 mg. orally per day in divided dosages. The 1:200 dilution has not been as effective as the 1:100 dilution while in the sanatorium.

Case 15.—J. B., aged sixty-six male, with bronchial asthma of four years' duration, had been in the hospital four days. During the previous two weeks at home his asthma had been resistive to all treatment. While in the hospital he continued to have two severe attacks daily with only slight relief from infusions of 0.5 gm. aminophyllin in 1,500 c.c. glucose-saline twice a day. He was started on inhalations

of 1.0 c.c. 1:100 every three hours, with immediate increase in his vital capacity following the first inhalation (Fig. 5). The day and night attacks did not recur. On the fifth day of treatment, because of a continued daily temperature spiking to 101 F., 50,000 units of penicillin were dissolved in each cubic centimeter of isuprel. His vital capacity continued to increase and at time of his discharge was 4.1 liters, which is a higher reading than would have been predicted in a man of his age. Since discharge he has used small amounts by inhalation nightly and occasionally during the day, and for two months has been free of attacks.

Case 22.—E. S., aged twenty-one, female, with bronchial asthma and intermittent eczema since birth, has had six lengthy Boston City Hospital admissions during the past three years. For twenty-four hours she was in severe asthma not relieved by four administrations of aminophyllin intravenously and one infusion of 5 per cent glucose in saline. She showed an immediate dramatic response when given 0.3 c.c. of 1:1,000 isuprel subcutaneously. The vital capacity improved from 0.8 liters to 2.4 liters in fifteen minutes and she changed from a wheezing, sick-appearing, sullen, uncommunicative girl to a smiling, talkative, much happier person. The cycle was broken by 0.25 c.c. injections of 1:1,000 subcutaneously every two hours for five doses and then every three hours. This was supplemented with 10 mg. orally every three hours. Forty-eight hours after this treatment she was started on oxygen-aerosol inhalations. In spite of marked irregularity of treatments, she managed to keep very comfortable. Since discharge she has used hand-bulb inhalations of isuprel with better results than were attained from many other drugs formerly used.

Case 28.—M. G., aged twenty-two, female, with a ten-year history of bronchial asthma, had frequent lengthy hospital admissions. Her present attack began at 6 p.m. on the day of admission and was not relieved by numerous injections of epinephrine at ten-minute intervals. Her physician gave her aminophyllin intravenously and she lapsed into unconsciousness and became deeply cyanotic. He administered artificial repiration and the fire department administered oxygen. She was then brought into the hospital and started on oxygen by face mask. She received 0.25 gm. aminophyllin intravenously on the admitting floor and arrived on the ward semiconscious and in great respiratory distress. Oxygen-aerosolization of 1.0 c.c. of 1:100 isuprel was administered with almost immediate dramatic relief. Full relief was observed in ten minutes and she had no further dyspnea the remainder of the night. She remained in the hospital for three weeks during which time dental extractions were made. She was completely comfortable on p.r.n. inhalations of isuprel. Since returning home, she has continued her hospital routine of taking small inhalations four or five times a day and 40 mg. orally in divided dosages. She finds this routine is far more effective than the previous home management of her asthma by epinephrine hypodermically.

SUBCUTANEOUS ROUTE

The 1:1,000 dilution by the subcutaneous route was studied in fifteen hospital patients. Twelve of these patients had chronic severe asthma and had been without relief in spite of varied intensive therapy over many hours. Eleven of these patients were epinephrine-fast and had been in status asthmaticus from four to seventy-two hours, averaging twenty-nine and six-tenths hours. One patient (Case 1), in his second admission under this program, had in the past failed to react favorably to epinephrine and other treatments when his attack entered the status state. The

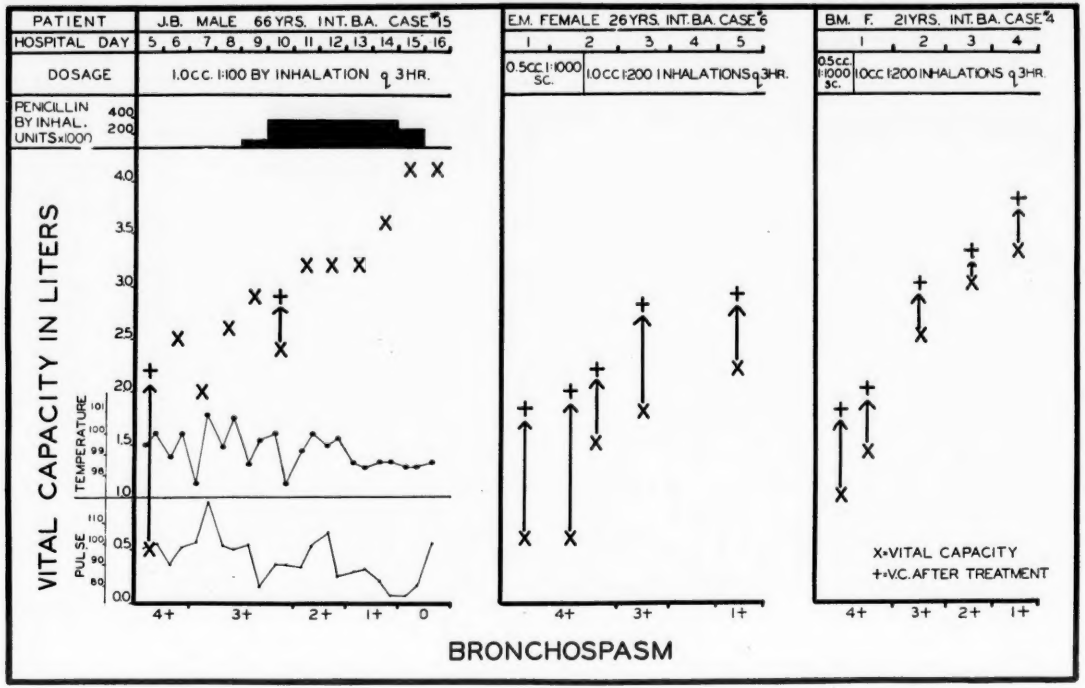

Fig. 5. Vital capacity recordings during hospital courses of three cases treated with isuprel by various routes.

other three patients had been in the hospital for varying lengths of time and, while not in status asthmaticus when treatment was instituted, were real therapeutic problems. The dosage varied from 0.25 to 0.75 c.c., with 0.25 c.c. of the 1:1,000 dilution appearing to give the best relief for dyspnea with the least side effects.

Eighteen vital capacity recordings were made. In each of the eighteen trials, including those for the eleven epinephrine-fast patients, these recordings show that the injection brought marked and immediate relief. This relief was usually noticeable within five minutes and reached its peak in about ten minutes. Figure 7 illustrates the average capacity before and after injections. There was an average increase of 1.18 liters in the eighteen trials, the smallest increase being 0.4 liters and the largest, 2.6 liters. Excluding the three patients not in status asthmaticus, the average increase in vital capacity following injections was 1.4 liters.

Unfortunately, the effects of the subcutaneous route were not long-lasting, and in two or three hours the patients usually required another injection in order to maintain the initial improvement. Its greatest effectiveness frequently appeared to be in breaking up the cycle of status asthmaticus although intensive therapy over the following twelve to twenty-four hours had to be given to retain the gains made. This may be done by repeating the subcutaneous dose every two hours for twelve hours or changing to oxygen-aerosolization of 1.0 c.c. of 1:100 dilutions every two to three hours, or using both, depending on the severity of the bronchospasm. Once the asthmatic cycle has definitely been broken, the patient is best treated with oxygen-aerosolization at gradually increasing intervals until discharge.

Since our preliminary report 0.25 to 0.5 c.c. of the 1:5,000 and 0.5 c.c. to 1.0 c.c. of the 1:10,000 dilutions have been used subcutaneously in seven patients. Although fewer side effects were noted and a moderate transient improvement was usually seen, the results were not as dramatic as those with the 1:1,000 dilution. The latter appears to be most effective in the initial active treatment of the very ill asthmatic who needs hospitalization.

ORAL ROUTE

Nine patients are taking oral isuprel in conjunction with hand-bulb inhalations. Most of these patients feel that the drug taken orally is not as effective as by inhalation. One patient, who has been in the hospital for four of the past five months, noted marked jitteriness and tachycardia on 50 to 80 mg. a day in divided dosage along with small inhalations p.r.n. When the oral drug was discontinued, his nervousness and tachycardia disappeared but he had to use the nebulizer more often to control his daily wheezing. In most cases the results are equivocal and it is impossible to evaluate them correctly at the time of this report. One hospital case was treated solely on oral medication of 80 to 120 mg. daily for a week

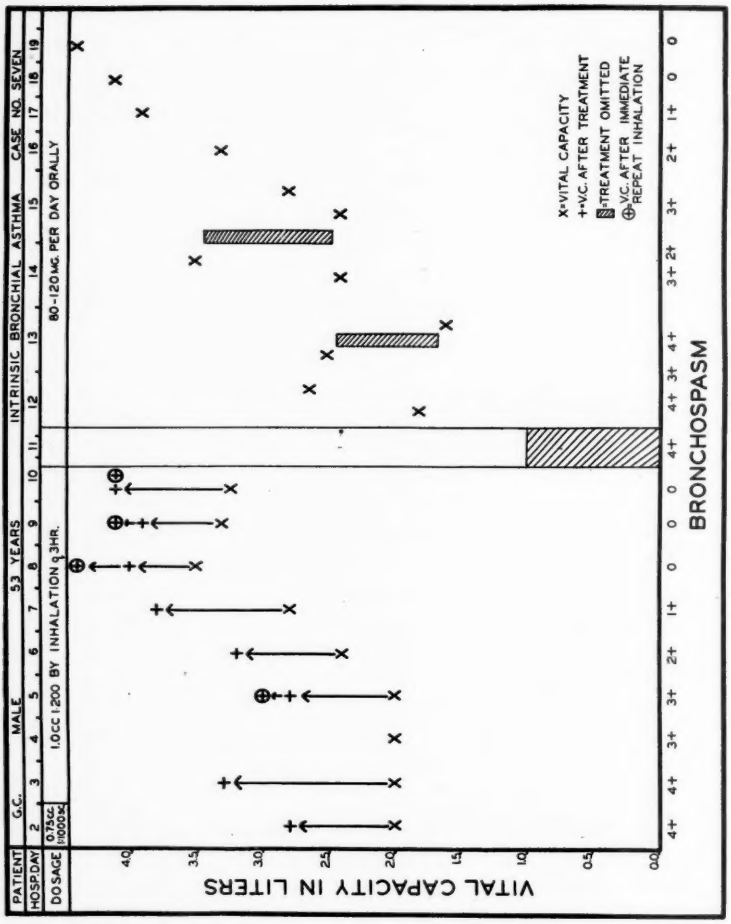
PATIENT G.C. MALE 53 YEARS INTRINSIC BRONCHIAL ASTHMA CASE NO. SEVEN
HOSP DAY 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19
DOSAGE 0.75cc 1:1000 SC
1.0CC 1:200 BY INHALATION q 3HR.
80-120 MG. PER DAY ORALLY
VITAL CAPACITY IN LITERS
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
4+ 4+ 3+ 3+ 2+ 1+ 0 0 0 4+ 4+ 3+ 4+ 3+ 2+ 2+ 1+ 0 0
BRONCHOSPASM
X=VITAL CAPACITY
+=VC. AFTER TREATMENT
=TREATMENT OMITTED
⊕=VC. AFTER IMMEDIATE REPEAT INHALATION

Fig. 6. Vital capacity recordings during hospital course (Case 7) treated with isuprel by various routes.

(Fig. 6). He had an excellent course but complained of persistent nervousness.

It might be said now that oral isuprel may have a place in the manage-

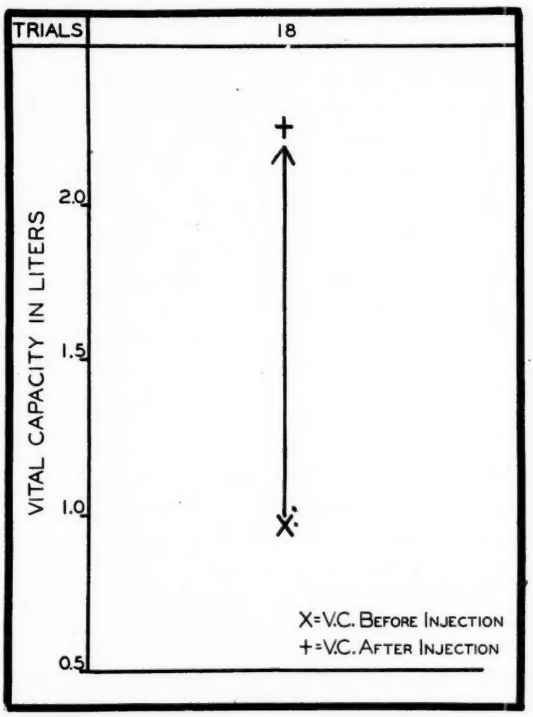

Fig. 7. Average of eighteen vital capacity recordings on fifteen hospital patients with moderate to severe bronchospasm using 0.25 c.c.-0.75 c.c., 1:1,000 isuprel subcutaneously.

ment of the chronic asthmatic who wheezes some every day but rarely has a severe attack. Its action appears to be two slow to warrant its use in the acute stage of asthma.

EFFECT ON BLOOD PRESSURE AND PULSE

The response of the blood pressure depends greatly on the amount of bronchospasm present. Osgood[12,13] in his discussion of the blood pressure fluctuations in bronchial asthma, has pointed out that such fluctuations are a constant finding, that their excursions depend upon the severity of the attack and that they signify the amount of respiratory obstruction present. The increased negative intrathoracic pressure during the forced and difficult inspiration period leads to a pooling of blood in the lungs and makes the filling of the left heart more difficult. This represents the low point in the fluctuations. Conversely, on expiration more blood is

sent to the left heart; therefore the systolic pressure is greater and the high point of the fluctuation occurs in this phase of the respiratory cycle. Since this fluctuation is an indirect measure of respiratory obstruction, its abolition may be considered an indication that less obstruction exists. Isuprel effectively abolished or markedly decreased this fluctuation and did so in an especially dramatic fashion when the bronchospasm was greatest. The results varied generally with the amount of bronchospasm present. When the spasm was 3+ to 4+ a marked drop towards normal levels was noted in both pressure phases. If the spasm was minimal, a moderate rise in the systolic reading and a corresponding fall in the diastolic was seen, a widened pulse pressure resulting.

Six studies of the blood pressure and pulse changes in five normal individuals were done. Three of the studies accompanied the 1:200 dilution by oxygen-aerosolization and three were carried out with the subcutaneous injection of 0.33 c.c. of the 1:1,000 dilution. The systolic pressure showed an average increase of 13 mm. of mercury with the inhalatory route and 22 millimeters with the subcutaneous route. The pulse pressure showed an average increase of 16 mm. of mercury with inhalation and 39 mm. with subcutaneous injection. The pulse increased an average of 18 and 50 beats per minute with the inhalatory and subcutaneous routes, respectively. This compares with Blumgart's studies[6] in ten normal subjects to whom 0.5 to 1.0 c.c. of 1:1,000 solution of epinephrine was given subcutaneously. He found an average rise in the systolic pressure of 38 mm. of mercury, an average increase in pulse pressure of 48 mm. of mercury and an average increase in the pulse rate of 16 beats per minute.

Isuprel, by the inhalatory route, caused minimal side reactions which disappeared quickly in the normal subjects. However, the subcutaneous injections in the normals led to marked palpitations, pounding, fullness in the chest and moderate headache. These symptoms began within two minutes and persisted to a disturbing degree for approximately one-half hour. The basal blood pressure and pulse levels were re-established shortly thereafter. The complaints of the patients following equal or larger amounts by subcutaneous injection were fewer than with the normals. Apparently the relief of their dyspnea was so outstanding as to cause less consciousness of the cardiovascular side effects which were paramount in the observations of the normal subjects.

A total of 118 recordings was made of the blood pressure and pulse changes accompanying oxygen-aerosolization and subcutaneous injections in the first twenty-nine hospitalized patients. Eighty-six recordings were made when various dilutions of isuprel were aerosolized by oxygen for varying degrees of bronchospasm. Thirty-two recordings were taken of the changes accompanying subcutaneous injection (Fig. 8.) The average widening of the pulse pressure in the 118 trials was only seven millimeters of mercury. In the thirty-two subcutaneous trials the pulse pressure increased by 10 mm. of mecury, while in the eighty-six oxygen-aerosolization record-

ings the increase was only 6 millimeters. The increase in pulse pressure in the asthmatics in this study is due almost entirely to a lowering of the diastolic phase. A peripheral vasodilation of the finer arterioles therefore

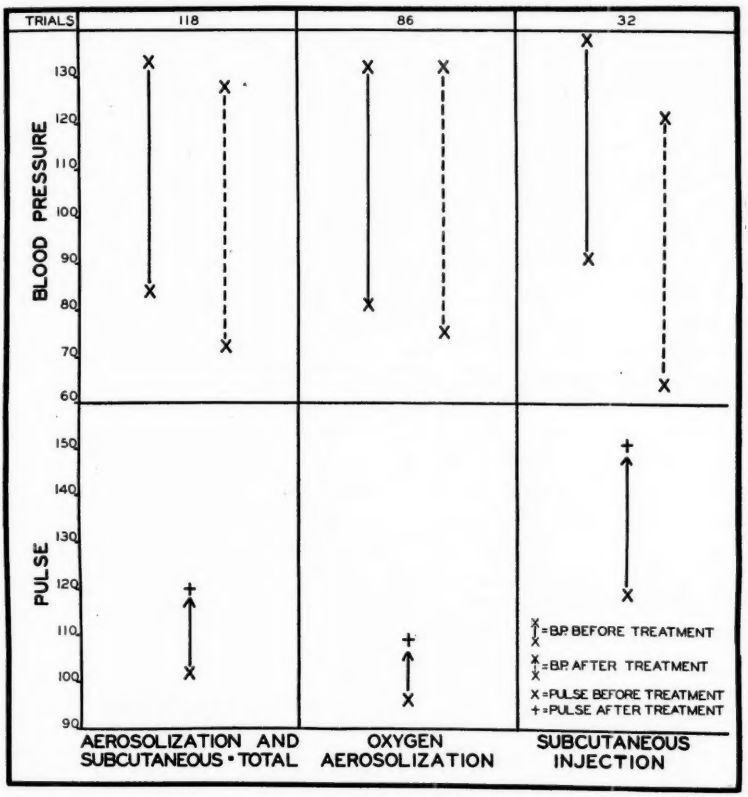

Fig. 8. Averages of 118 recordings of the blood pressure and pulse changes occurring with various dilutions of isuprel by oxygen-aerosolization and subcutaneous injection in twenty-nine hospital patients.

probably occurs, implying an excess of the sympathin I fraction. The pressor action observed with epinephrine, which is due to a predominance of sympathin E and is especially disturbing to hypertensives, appears to be present to a lesser degree with isuprel.

The average increase in pulse in the total group is from 102 to 120 beats per minute. Considered separately, the subcutaneous route caused a jump in the pulse rate from 119 to 151, an increase of 32 beats per minute, while the oxygen-aerosol route showed a lesser change from 96 to 109, an increase of 13 beats per minute (Fig. 8).

The differences in blood pressure and pulse changes (Fig 8) between

the oxygen-aerosolization and subcutaneous routes are due to the fact that the inhalatory group represents a mixture of all degrees of bronchospasm from 1+ to 4+, while all the patients receiving the subcutaneous isuprel were in 3+ to 4+ bronchospasm. For all practical purposes, the results noted with subcutaneous injections are also seen where extreme bronchospasm is treated by oxygen-aerosolization. Observations on the eleven patients treated since the original report are in conformity with the above as regards the blood pressure and pulse changes.

SIDE REACTIONS

Table I illustrates the general type and frequency of side reactions noted in (1) 187 individual oxygen-aerosolization trials on eighty-two ambulatory patients and (2) more lengthy observations over a period of days in the first twenty-nine hospitalized patients treated by both the oxygen-aerosol and the subcutaneous routes. The inhalatory route is generally very benign as far as undesirable side reactions are concerned. The majority of the ambulatory patients had either no reactions or slight jitteriness or palpitations which wore off quickly. The oxygen-aerosol route in the hospital cases showed essentially the same benignity and not one patient felt that these reactions detracted from the relief of his dyspnea. More serious reactions—marked palpitations being the most outstanding—were seen from the subcutaneous route, especially if the 1:1,000 dilution was used in doses of 0.5 c.c. or more. Five patients also showed nausea and vomiting but three had these symptoms before the treatment. In general, 0.20 c.c. to 0.33 c.c. of 1:1,000 produced the best relief of dyspnea with minimal side effects. Seven patients were given frequent subcutaneous injections with no cumulative effect noted. Very few of the undesirable side reactions persisted for more than five to fifteen minutes. As noted above, the smaller dilutions by injection caused fewer side effects but were less effective in aborting dyspnea.

Only a few observations can be made in this report regarding ill effects of oral isuprel. Attendant nervousness and tachycardia have been observed with doses above 50 mg. daily. These symptoms wore off quickly when the drug was omitted and did not reappear with the smaller doses.

CONCLUSIONS

1. Isuprel (1-(3,′ 4′-Dihydroxyphenyl)-2-isopropylaminoethanol), a new pneumodilator drug, appeared to be effective in relieving the dyspnea of bronchial asthma.

2. Three routes of administration were employed: oxygen-aerosolization, with doses of 1.0 c.c. of 1:100 dilution every three hours; subcutaneous, with doses of 0.20 to 0.33 c.c. of 1:1,000; and oral with doses of 30 to 60 mg. daily. These dosages were generally the most effective in their respective routes of administration.

3. Results are presented of 187 trials in eighty-two ambulatory patients

treated by oxygen-aerosolization and in forty hospitalized patients treated by one route alone or by a combination of routes.

4. Subjective relief from bronchospasm was observed and correlated with improvement in the vital capacities. The greater the degree of bron-

TABLE I. SIDE REACTIONS

Reaction	Ambulatory Patients	Hospital Patients		
			Subcutaneous	
	Oxygen Aerosol	Oxygen Aerosol	0.5–0.75 cc.	0.25 0.33 cc.
None	149	8	..	..
Palpitation				
Slight	10	8	1	4
Moderate	4	4	1	3
Marked	2	1	6	1
Dizziness				
Slight	..	1	3	1
Moderate	..	1	1	1
Marked	..	..	1	..
Jittery				
Slight	7	3	1	..
Moderate	2	..	..	..
Marked	5	..	1	..
Headache or Throbbing	2	2	1	1
Euphoria	1	..	..	..
Nausea	..	1	4	1
Vomiting or Retching	..	..	5	1
Epigastric Pain	..	..	1	..
Sweating	1	..	1	..
Flush	..	..	..	1
Precordial Pain	..	..	1	..
"Filled Up"	..	2	..	..
Dryness of Mouth	4	..	..	..
Sore Tongue or Mouth	..	2	..	..
Tingling of Lips	..	..	1	..
Pink Sputum	..	2	..	..

chospasm, the greater was the improvement in vital capacity. This improvement was also observed in patients with coughing paroxysms who were free of bronchospasm.

5. The fluctuations in blood pressure observed in asthmatics, namely, the variation in the systolic and diastolic readings in inspiration and expiration, were effectively abolished or markedly decreased and in an especially dramatic fashion when the bronchospasm was greatest.

6. Undesirable pressor effects and tachycardia were minimal and in general corresponded to the individual's tolerance to sympathomimetic amines. Reactions may be alarming if more than 0.5 c.c. of 1 :1,000 is given

subcutaneously. The drug should not be used intravenously. Sensitive patients should get inhalatory doses of 0.5 c.c. of the 1:200 dilution and subcutaneous doses of 0.1 c.c. of the 1:1,000 dilution. These doses may be gradually increased to determine individual tolerance.

7. The epinephrine-fast state observed in eleven patients responded favorably. No fastness to isuprel was observed.

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NORTHWEST POLLENS

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IN considering pollens of the Northwest, one is confronted with the flora of two distinct climates. If one checks the charts in most of the books on allergy, including the *Manual of Allergy Laboratory and Diagnostic Procedures,* as put out by the American College of Allergists, he finds the plants under one heading for northern California, northern Nevada, the whole state of Oregon and the whole state of Washington. Vaughan[3] considers western Washington, western Oregon and northern California separately, and the floras of each area are found to be entirely different; although the pollinating dates are inaccurate for the Washington area, it does give a truer picture.

If one looks at the topography of the northwestern states and considers the source of their weather, he immediately sees the reason for such a marked difference of climate and flora within a few miles. The Cascade range of mountains roughly parallels the coast 100 miles inland, and is the true dividing line (Fig. 1). This range is very high, with such peaks as Mount Baker, Mount Rainier, Mount Hood and Mount Shasta, with elevations up to 14,408 feet. During the months of January and February, there is a prevailing southeast wind, but the storms actually come from the southwest, which would bring them from over warm ocean currents. Thus, as this warm moist ocean air nears the high cold Cascades, there is condensation and, therefore, marked rainfall. Seattle, which is eighty-five miles inland, has an average rainfall of 33.28 inches, and Wenatchee, which is just thirty miles east of the divide, has 8.75 inches of rainfall. In Oregon, Portland, approximately sixty miles from the coast, has an annual rainfall of 41.62 inches; Eugene, fifty miles inland, has 37.83 inches; and Bend, just twenty-five miles east of the divide, has 12.72 inches of annual rainfall.

One would expect cold winter months at this latitude, but heavy frosts are not common even as far north as Juneau, Alaska. During March, April, May and June, the winds are generally from the south with less moisture, and there is considerable warm weather which is conducive to rapid plant growth. However, at the height of the summer season, July, August and September, the winds shift, coming from the north, off the Bering Sea area and the North Pacific, tempering the summer climate. This type of season, it is thought, is not conducive to maturing the usual fall weeds in this area. In October, November and December the air currents again come from the southwest but, due to the fact that they travel circularly, counterclockwise, the prevailing winds again are from the southeast. For these reasons, the 100-mile-inland coastal strip of Oregon and Washington has a very mild winter and moderately warm

Lecture presented March 6, 1946, American College of Allergists, Regional Spring Instructional Course, University of Oregon Medical School, Portland, Oregon.

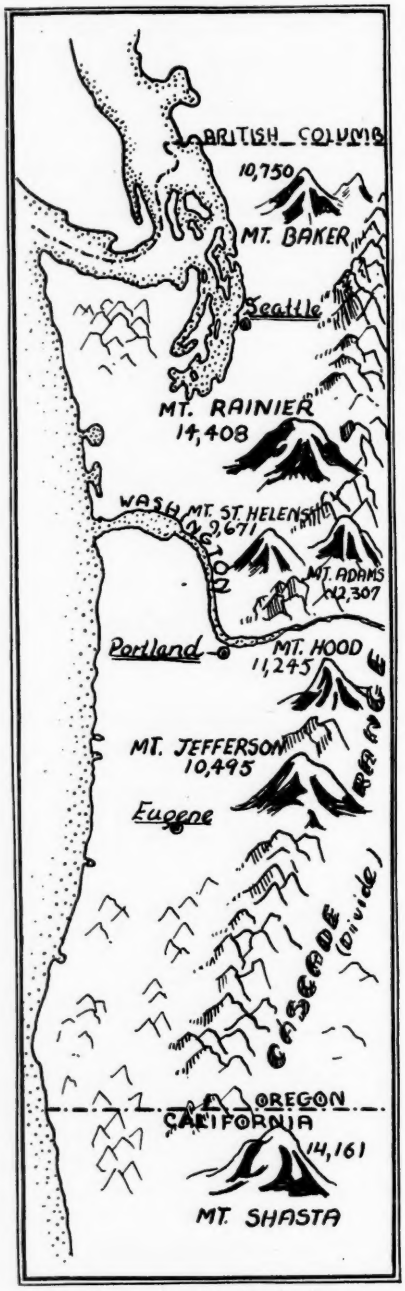

Fig. 1. Topography of Pacific Northwest area.

summer. In the areas east of the Cascade range, the climate is midwestern in nature, with hot dry summers and cold snowy winters. The fall season is again ideal for weed growth; short ragweed *(Ambrosia*

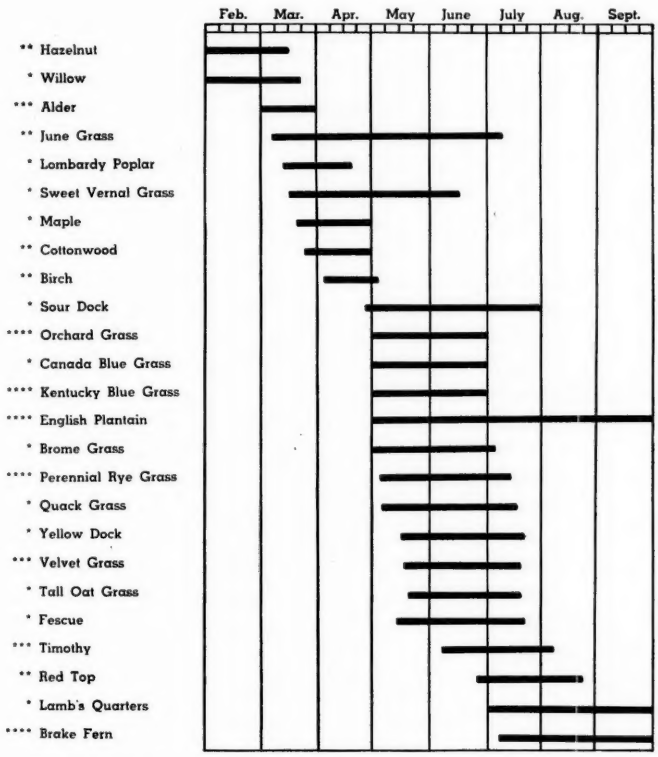

Fig. 2. Pollinating dates of hay fever plants in Seattle. Asterisks indicate relative pollen concentration.

elatior), western ragweed *(A. psilostachya)*, giant ragweed *(A. trifida)*, desert sagebrush *(Artemisia tridentata)* and Russian thistle *(Salsola pestifer)* are present.

In speaking of Northwest pollens, allergists who practice along the coast think chiefly in terms of pollens within the coastal area, which would hold from northern California to Juneau, Alaska. They think of the pollens east of the Cascade range as midwestern. I will include some of the important offenders east of the Cascades.

The Seattle pollen season begins about the first of February (Fig. 2) with willow *(Salix scoleriana)* and hazelnut *(Corylus californica)*. *Salix lasiandra and S. sitchensis* are not prevalent. Due to the facts that willow pollen is partly insect-borne and that rains are prevalent during their

anthesis, it cannot become a serious offender in the northwest area. South of Portland, there are large groves of hazelnuts. The one most commonly grown is *Corylus avellana,* occurring in its several varieties.

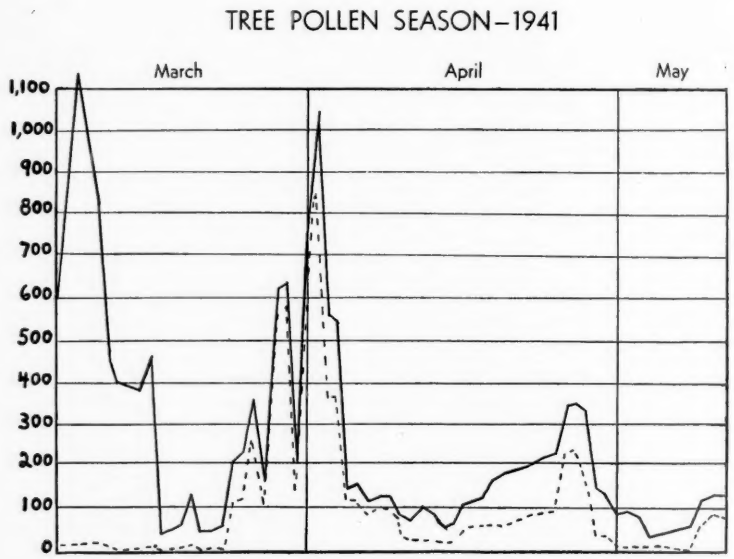

Fig. 3. Pollen grains per unit slide area (1.8 sq. cm.). Dotted line represents the pine season.

White aveline, Barcelona, Daviana, and Du Chilly are others. The pollinating dates vary according to the variety, extending over a period of about ten weeks. In this area, spring hay fever is definitely increasing, proving the potency of tree pollen when present in large quantities. In this same area, black walnut *(Juglans nigra)* and English walnut *(J. regia),* which can be offenders, pollinate from late March through April.

Alder *(Alnus oregona)* starts pollinating about March 1, reaching a peak sometime between March 10 and 20. This peak is one of the highest of any season and may reach a count of 1,000 or more per 1.8 sq. cm. per day (Fig. 3). It is not unusual in the spring to find patients sensitive only to alder pollen, and status asthmaticus is not uncommon at this time of the year. Elm *(Ulmus americana)* and the Lombardy poplar *(Populus nigra),* an introduced species, are not very common. The maples *(Acer macrophyllum* and *A. rubrum)* are partly insect-pollinated and probably not important. The cottonwood *(Populus trichocarpa)* does not pollinate over a long enough period of time to be a serious offender. The aspen *(P. tremuloides)* is relatively scarce. These pollinate in late March. In the early part of April, birch *(Betula pendula)* pollinates and is next in importance to alder among the trees.

(B. fontinalis) is more common in eastern Washington. Sycamore *(Plantanus acerifolia)* appears only in scattered areas throughout the cities, and the ash *(Fraxinus oregona)* is not common. Box elder *(Acer*

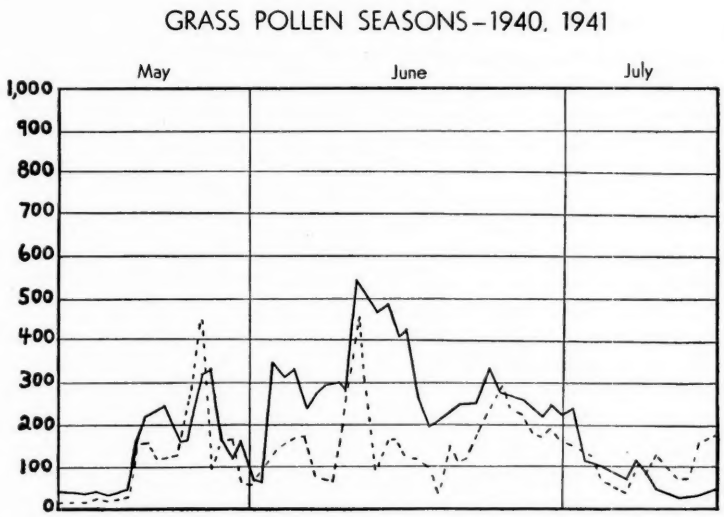

Fig. 4. Pollen grains per unit slide area (1.8 sq. cm.). Solid line is for 1940, and dotted line is for 1941.

negundo) and locust*(Robinia pseudoacacia)* are sparingly present in the area east of the mountains. Oak *(Quercus garryana)* appears scattered over the flat lands throughout the northwest and is a factor where abundant. Numerous, introduced, ornamental trees and shrubs, such as dogwood *(Cornus nuttallii)*, common Indian plum *(Osmaronia cerasiformis)*, mountain ash *(Sorbus americana)* and red flowering currant *(Ribes sanguineum)*, are of doubtful importance, if ever a factor. A large variety of conifers grow in this district, but they do not seem to contain an excitant factor. In the eastern part of the state yellow pine *(Pinus ponderosa)* has been reported to be a factor.[1] However, Seattle pine pollen counts during the season of 1941 rose to 1,000 per 1.8 sq. cm. (Fig. 3), and many newspaper articles appeared telling of the clouds of yellow pollen and "sulphur" streams; even the birds of the forest were yellow with pollen. Scouring rush *(Equisetum telmateia)* sporulates heavily in certain coastal areas from March to May. It is a menacing weed and its spores appear frequently on the slides, but I have never found it to be a factor in hay fever.

The grass season starts moderately about April 1, with low speargrass *(Poa annua)* and sweet vernal grass *(Anthoxanthum odoratum)*. The latter is distinguished by its pleasant, sweet odor. The season becomes in-

tensified about May 15, reaching its height during the early part of June and declines by July 15 (Fig. 4). Many grasses pollinate in small quantities until October. Canada blue grass *(P. compressa)* and Kentucky blue grass *(P. pratensis)* start about May 1. The latter is one of the widely distributed grasses in this area and a major offender. English plantain *(Plantago lanceolata)* starts as early as May. Like other weeds, it is not found to be allergenic as often as the grasses, but is potent and can be the only offender in some cases during July and August. Greater plantain *(P. major)* is rather scarce. Quack or wheat grass *(Agropyron repens)*, perennial rye *(Lolium perenne)* and Italian rye *(L. multiflorum)* also flower at this time. The other ryes, such as *Elymus hirsutus, E. glaucus, E. mollis,* and *E. canadensis,* are less abundant but will likely become more important in the future. *Bromus sterilis, B. mollis, B. marginatus, B. carinatus, B. ciliatus* and *B. racemosus,* are fairly common and are increasing in abundance. Orchard grass *(Dactylis glomerata)* is widely distributed and bears one of this area's most potent pollens. Tall oat grass *(Arrhenatherum elatius)* appears as large plumes along the graded roadsides and is increasing in abundance. Velvet grass *(Holcus lanatus)* is rather a showy grass with silvery colored leaves, and is one of the chief offenders. Smooth velvet *(H. mollis)* is sparsely distributed. Timothy *(Phleum pratense)* and most of the fescues *(Festuca)* start pollinating about July 1. There are many of the latter (some without common names), namely, *F. myuros,* rat's-tail fescue; *F. subulata,* bearded, fescue; *F. octoflora,* six-weeks fescue; *F. dertonensis; F. elatior,* meadow fescue; *F. ovina,* sheep fescue; and *F. rubra,* red fescue. *F. elatior* and *F. dertonensis* are probably the most important of this group. The barleys, *Hordeum murinum, H. jubatum* and *H. nodosum* are flowering at this time, but the quantity of pollen that they shed is so small that they cannot be considered important. Crested dogtail *(Cynosurus cristatus)* and Koeler's grass, or June grass, *(Koeleria cristata)* are on the increase and, no doubt, will become more important. Red top *(Agrostis alba)* and bent grasses *(A. maritima* and *A. tenuis)* start pollinating during the later part of June. It is not unusual to see a field that was silvery in color from velvet grass become a brownish red a few weeks later due to red top, giving the impression that the former grass has dried and gone to seed. Other minor grasses belonging to this genus are the creeping bent *(A. palustris)*, water bent *(A. verticellata)* and spike red top *(A. exarata)*. Other grasses, of little or no importance, are slender hair grass *(Deschampsia elongata)*, tufted hair grass *(D. caespitosa)*, annual hair grass *(D. danthonioides)*, rabbits' foot grass *(Polypogan monspeliensis), rice cut grass (Leersia oryzoides)*, silver hair grass *(Aira caryophyllea)*, and crab grass *(Digitaria sanguinalis)*, which looks like the common Bermuda grass of the South.

Grama, Bermuda and Johnson grasses do not grow in the Northwest. The weed, barnyard grass *(Echinochloa crusgalli)*, is fairly abundant in some areas east of the Cascades.

The weed pollen season for the coast is of minor importance as compared to the other seasons. Yellow dock *(Rumex crispus)*, bitter dock *(R. obtusifolius)* and sheep sorrel *(R. acetosella)* have a wide distribution but are not abundant. These three pollinate together with the grasses in May and June, but I get few allergic reactions to them in testing.[2] Lamb's quarters *(Chenopodium album)*, pigweed *(Amaranthus retroflexus)* and mugworts *(Artemisia vulgaris* and *A. heterophylla)* gave strongly positive reactions at times and must be considered. Burweed marsh-elder *(Iva xanthifolia)*, nettle *(Urtica lyalli)*, and cockle bur *(xanthium)* grow here, but rarely do I get positive reactions from their pollen.

The commonest weed east of the Cascades is Russian thistle *(Salsola pestifer)*, which pollinates from mid-June to mid-September. In eastern Oregon, sagebrush *(Artemisia tridentata)* is the commonest in some areas. Mountain sage and prairie sage are seldom found. Western water hemp *(Acnida tamariscina)* and Marsh elder *(Iva xanthifolia)* are factors in some areas. Mugwort *(Artemisia vulgaris)* and wormwoods, usually *A. vulgaris* and *A. heterophylla*, also salt bush *(Atriplex truncata)*, are found occasionally. These are factors in hay fever, and pollinate from mid-June to late fall. Western ragweed *(Ambrosia psilostachya)* and false ragweed *(Franseria acanthicarpa)* are found, as is a little short ragweed *(Ambrosia elatior)*. These are increasing in abundance east of the Cascades, but do not compare in importance with Russian thistle and sagebrush.

The ferns shed an abundance of spores in August and are found growing everywhere in the Puget Sound area. The total spore count almost equals that of the grasses.[2] However, I can say that I have never seen a true case of fern-spore hay fever. The common brake, or bracken *(Pteridium aquilinum)* produces over 90 per cent of the spores found. The spores of this and the sword fern *(Polystichum munitum)* are easliy distinguished from the pollen grains on the slides. Other species are not common.

I wish to express my indebtedness to Dr. G. N. Jones, formerly in charge of the University of Washington Herbarium, for the identification of numerous plants; to Dr. C. Leo Hitchcock, of the University of Washington and to Dr. Helen M. Gilkey of the Oregon State College, for their information on plant distribution and pollinating dates.

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A limited number of the comprehensive abstracts of the lectures, which were presented at the Fall Graduate Instructional Course in Philadelphia in November, 1946, are available at $6 per set. Each set is composed of forty-three printed lectures, which are perforated for a standard ring book and thus form an up-to-date manual of allergy, with complete bibliography.

SKIN TESTING WITH FRACTIONS OF CHOCOLATE

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Brooklyn, New York

CHOCOLATE is one of the most common food offenders among allergic individuals. Nevertheless the incidence of positive skin reactions to chocolate is not very large. Moderate or marked skin reactions with this allergen are not common. Clinically however, many allergists and pediatricians eliminate chocolate routinely from the diets of their allergic patients and note some degree of improvement in many of them.

This study was undertaken to determine whether the skin reactions would vary if the skin were tested with extracts of the different parts of the cocoa bean and with extracts of the various finished chocolate and cocoa products.

Chocolate is derived from the cocoa bean. The bean is roasted first and then crushed. The resulting product is known as cocoa nibs. The shells are separated from the cocoa nibs by a rotating process. Better grades of chocolate are practically free of shell. Shells are considered as adulterants and are used as cattle feed. The nibs are ground and milled thoroughly to a thin paste which on cooling forms a hard cake. This is known as cocoa liquor or plain chocolate. By extracting 50 per cent or more cocoa butter from the liquor, press cakes result. These are pulverized to give cocoa powder.

TABLE I. COMPOSITION OF CHOCOLATE

Type	Per Cent Chocolate Liquor	Per Cent Sugar	Per Cent Total Fat	Per Cent Whole Milk Solids
Bitter	100	0	50–56	0
Bittersweet	80–95	5–20	40–50	0
Darksweet	25–45	40–50	34–42	0
Lightsweet	5–15	55–68	31–39	0
Sweetmilk	7–17	35–55	28–39	12–20

There are many types of chocolate available on the market. There is bitter chocolate which is pure chocolate without the addition of sugar or other ingredients, and this is commonly called chocolate liquor. This chocolate liquor is used as a base for the manufacture of sweet and milk chocolate by the addition of sugar, milk, flavors and other ingredients. To make the chocolate fluid, various amounts of cocoa butter are added to the mixture.

The composition of chocolate varies in its content of chocolate liquor, sugar and other ingredients in the mixture. The approximate compositions of common types of chocolate are given in Table I.

From the Allergy Clinic of the Beth Moses Hospital.
The various chocolate products were supplied through the courtesy of Rockwood Chocolate Company of Brooklyn.

TABLE II. INTRACUTANEOUS TESTS

	Clinically Chocolate Sensitive	Cocoa Bean	Cocoa Shell	Cocoa Nib	Cocoa Liquor	Cocoa Powder	Control Saline
1 R L	+	0	0+	0	0+	0	0
2 N Z	+	Sl	Sl+	0	0	0+	0
3 B L	0	0	0	0	0	0	0
4 F F	+	Sl—	Sl	0+	0	Sl—	0
5 Y S	0	Sl—	Sl—	Sl—	Sl	Sl—	0
6 Y T	0	Sl	Sl	Sl—	Sl—	Sl—	0
7 R P	0	0	0	0	0	0	0
8 H H	0	Sl	Sl	0	0	0	0
9 R G	0	0	0	0	0	0	0
10 M C	+	0+	0	0	0	0	0
11 J S	+	0+	0	0	0+	0	0
12 M L	+	Sl—	Sl+	Sl—	Sl	Sl	Sl—
13 M S	+	0	0+	0	0	0	0
14 Y S	+	Sl	Sl—	0	0	0	0
15 W W	+	Sl—	Sl—	Sl—	Sl—	0+	0+
16 E G	0	0	0	0	0	0	0
17 D B	+	Sl	MKD	Sl—	0	0	0
18 N D	0	Sl	Sl+	Sl—	0	0	0
19 K	0	0	Sl	0	0	0	0
20 B S	+	Sl—	Sl—	0	0	0	0
21 R G	+	Sl++	Sl+	Sl	Sl+	Sl—	0
22 S H	+	Sl	Sl—	0+	0	0	0
23 R C	0	0	0	0	0	0	0
24 J P	+	0	0	0	0	0	0
25 R L	+	0	0	0	0	0	0
26 K G	+	Sl—	0	0	0	0	0
27 N P	+	0	0	0	0	0	0
28 I K	0	Sl—	0	Sl—	0	0	0
29 O R	+	0	0	0	0	0+	0
30 Z K	+	0	0+	0	0	0	0
Summary:							
Skin Reactions:							
Slight Minus		7	5	7	2	4	1
Slight		7	4	1	2	1	0
Slight Plus		1	4	0	1	0	0
Mod. to Marked		0	1	0	0	0	0
Totals		15	14	8	5	5	1

O=Negative reaction SL—=More than negative, less than slight
SL=Slight positive reaction SL+=More than slight positive, less than moderate

Chemically, chocolate consists of cocoa butter, sugar, moisture and cocoa solids. The cocoa solids consist of:—

crude fiber
ash
cocoa starch
other digestible carb.
caffeine
theobromine
nitrogen
protein

manganese
copper
chlorides
sulphates
cocoa tannin
pectin
cocoa red

organic mineral constituents
phosphorous pentoxide
silica
lime
magnesium oxide
potash
soda
ferric oxide
alumina
tartaric acid
acetic acid
citric acid
oxalic acid

In order to determine whether the skin reaction varied when different parts of the bean were used for testing, extracts were made with cocoa

TABLE III. PASSIVE TRANSFER STUDIES WITH FOUR SUBJECTS

	Subject Sensitized	Subject Tested	Cocoa Bean	Cocoa Shell	Cocoa Nib	Cocoa Liquor	Cocoa Powder
S. Serum	11/6/44	11/9/44	Sl-mod	Mod	Sl	Sl-mod	Sl
G. Serum	11/6/44	11/9/44	0	0	0	0	0
N. Serum	10/30/44	11/3/44	Sl+	Sl+	Sl	Sl+	Sl—
R. Serum	10/30/44	11/3/44	Sl—	Sl—	Sl—	0	Sl

bean, shells, nibs, liquor and powder. Extracts were prepared in the usual manner. They were ground, defatted first with toluol and then washed four times with water-free ether. To the dried defatted powder, buffered saline was added and covered with toluol. After seven days the extract was filtered.

Thirty atopic cases were tested with these extracts by the intracutaneous method using 0.1 mg. concentration. There were nineteen cases with positive clinical history of chocolate sensitivity and eleven with negative histories (Table II).

The skin reactions in this series were predominantly slight-minus to slight. Occasionally a slight-plus and in one instance a marked reaction was obtained. Cocoa bean and cocoa shell gave the greatest number of positive reactions. There was no definite correlation between clinical symptoms and positive skin reactions.

Four cases were selected with marked clinical histories of chocolate sensitivity. These cases developed allergic symptoms within one-half to two hours after ingestion of chocolate. Serum was obtained from these individuals and passive transfer studies were made using same extracts as in Table II. In one case we failed to get any positive reaction in spite of the positive clinical history. The other three cases gave slight to moderate reactions (Table III).

Since there was no marked difference observed in testing with the various parts of the cocoa bean, we thought it advisable to perform skin tests with various chocolate and cocoa products sold to the consumer. The following extracts were thus prepared:

1. Natural Breakfast Cocoa No. 5—natural cocoa powder prepared by extracting cocoa butter. This contains about 22 per cent butter fat.
2. Natural Solvent Extracted Cocoa Powder No. 6—low fat—contains about 0.20 per cent total fat.
3. Semi-sweet chocolate, dark No. 8—prepared by blending sucrose, chocolate liquor, flavor and sufficient cocoa butter to make it fluid. It contains about 33 per cent cocoa butter and vegetable lecithin.
4. Light-sweet chocolate coating No. 9—contains about 32 per cent cocoa butter and 64 per cent sugar.
5. Natural chocolate liquor No. 10—contains between 52 to 56 per cent cocoa butter.
6. Sweet milk chocolate No. 12—low in chocolate liquor, high in total fats and moderately high in dry whole milk constituents.

TABLE IV. TESTS WITH EXTRACTS OF CHOCOLATE PRODUCTS

Name	Clinical Positive	Natural Breakfast Cocoa No. 5	Natural Solvent Extracted Cocoa No. 5	Semi-Sweet Chocolate No. 8	Light Sweet Chocolate Coating No. 9	Natural Chocolate Liquor No. 10	Sweet Milk Chocolate No. 12
1 R G	+	0	0	0++	0++	0++	0++
2 M O	0	0	0	0	0	0	0
3 E N	+	0	0	0	0	0	0
4 E S	+	0	0+	0	0	0	0
5 M J	+	0+	0++	Sl	0+	0++	0+
6 B Z	0	0	0+	0	0	0	0
7 L M	0	0	0+	Sl—	0	0+	0+
8 B W	+	0++	0+	0++	0++	0+	0++
9 C M	+	Sl	0++	0	0	0++	0++
10 A F	+	0	0	0	0	0	0
11 A A	+	Sl	Sl	Sl+	Sl	Sl	Sl—
12 J K	+	0	0	0++	0+	0	0+
13 A L	0	0	0+	0	0	0	0
14 S L	0	0	0	0+	0	0	Sl
15 T W	+	0	0	0	0	0	0
16 I H	0	0	0	0	0	0	0+
17 P L	0	0	0+	0	Sl	0	0++
18 L W	+	0+	0	0++	0	0	0++
19 E M	+	0	0+	0	0	0+	0
20 J L	+	0++	Sl+	0++	0++	0	0
21 L G	+	0	0+	0	0	0+	0
22 H K	0	0	0	Sl—	0	0	Sl+
23 H F	0	0	0	0	0	0	0
24 K L	+	0	0	0	0	0	Sl
25 M K	0	0	Sl	Sl	Sl	Sl+	Sl—

0 =absolutely negative
0+ =slightly more than negative
0++ =a degree more than 0+

Sl— =a little less than slight
Sl =slight
Sl+ =more than slight

Twenty-five allergic individuals were tested with extracts of the finished chocolate products commonly used. The skin reactions were negative to slight and did not show any variations, regardless of the type of extract used (Table IV). There were fifteen patients in this series who were chocolate sensitive clinically, and ten were negative.

DISCUSSION

An attempt has been made to ascertain why a substance like chocolate which is a common food in our daily diet produces allergic manifestations so frequently and yet on skin tests fails to give positive skin reactions in a great many instances and rarely more than a slight reaction in most cases. Many allergists routinely remove chocolate from the diet of their allergic patients regardless of the results of the skin tests and note definite improvement in their patients. There is no standard method of preparing chocolate extracts today. Cocoa bean and various chocolate bars are used by allergy clinics in the preparation of their antigen. It was thought advisable to assay the various types of chocolate extracts using different parts of the cocoa bean and also finished chocolate products commonly ingested by the individual patient and to determine which extract is most suitable for skin testing. From the viewpoint of skin tests, it seems best to use the cocoa bean in the preparation of the chocolate extract. For, with the bean extract the percentage of positive skin reaction is somewhat better. Regardless of the type of chocolate extract used there is no definite correlation between clinical sensitivity and skin tests. In some

of our cases where there was definite clinical sensitivity we obtained a negative or slight skin reaction. In other cases with negative sensitivity, slight or slight-plus reactions were elicited.

This work gives further evidence of the great pitfall in depending on skin tests for clinical sensitivity. What is true of chocolate is likewise true of many other foods. Great caution should therefore be exercised in evaluating skin tests, whether positive or negative, particularly when dealing with essential and basic foods. The unnecessary elimination of some of these foods often aggravates the condition of the patient, resulting in marked loss of weight. On the other hand a slight reaction may be of definite significance. Clinical trials of suspected foods and careful daily diaries will help establish true clinical sensitivity.

In our next experiment we will attempt to hydrolyze chocolate with pepsin, acid, and alkalies in an effort to note whether the split products of chocolate react differently on the skin of individuals who are clinically sensitive to chocolate.

CONCLUSIONS

1. Chocolate extracts made from cocoa bean and cocoa shell gave more positive skin reactions than nibs, liquor or cocoa powder.
2. No definite correlation exists between skin reactions to chocolate and clinical symptoms.

I am indebted to Dr. J. Kahn and Dr. A. Kantrowitz for their assistance.

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STANDARDIZATION OF POLLEN EXTRACTS

(Continued from Page 296)

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SENSITIVITY TO THIAMINE HYDROCHLORIDE
Report of a Case

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VARIOUS types of reactions following the administration of thiamine hydrochloride have been reported during the past seven years. These reports attribute the reactions to the administration of thiamine hydrochloride to patients who had previously taken this substance with no ill effect. Skin tests have been recommended as a precautionary measure when the parenteral administration is contemplated.[1,3]

We have recently seen a case of sudden collapse following the intramuscular injection of 50 mg. of thiamine hydrochloride. This patient and seventy-three controls were tested with various dilutions of the vitamin.

CASE REPORTS

In January, 1944, a previously healthy thirty-two-year-old seaman returned from a trip during which he had been engaged in repeated bombing attacks. He noticed nervousness, insomnia, loss of appetite, tremor of his hands and a startle reaction to sudden noises.

He received treatment in several cities for these symptoms and thiamine hydrochloride injections were given frequently. For three weeks following April 20, 1944, he was given 100 mg. intramuscularly every other day. During May and June of 1944 he received approximately ten injections of unknown dosage. From July 16, 1944 to August 4, 1944, he was given injections of 100 mg. every other day. On August 30, 1944, several minutes after an intramuscular injection of 50 mg. of thiamine hydrochloride, he developed severe itching and redness of his skin and eyes, dryness of the throat, severe shortness of breath with wheezing respirations and collapsed. He recovered thirty minutes after administration of epinephrine. He was then sent to us for further study.

There was no history of allergy in the patient or his family. The physical findings were entirely normal. The blood smear showed 4 per cent eosinophiles.

SKIN TESTS ON THE PATIENT

Skin tests were done on the patient and on seventy-three controls. All tests were read as follows:

4+ Pseudopods, wheal and flare
3+ Wheal and flare
2+ Flare 1 cm. or greater
1+ Flare less than 1 cm.
0 Same as saline control

Intradermal tests on the patient, with two brands of thiamine hydrochloride and with a solution of thiamine hydrochloride in physiological saline, were positive (4+) in dilutions of 50, 10, 5, 2.5, and 1 mg. per

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Permission for publication given by the Surgeon General, U. S. Public Health Service.

c.c. Scratch tests with a solution of thiamine hydrochloride in physiological saline were positive in dilutions of 50, 10, 5 and 1 mg. per c.c. (4+, 4+, 3+, and 3+ respectively). Saline control tests were negative. Passive transfer tests gave a positive (4+) reaction in the 50 mg. per c.c. dilution but more dilute solutions were negative as compared to controls on the recipient.

Intradermal tests repeated after fifteen months during which the patient had no thiamine gave completely negative results in all dilutions.

TABLE I.

Degree of Reaction	Concentration in mg. per c.c.				
	50	25	10	5	1
4+	2	2	0	0	0
3+	4	3	0	0	0
2+	10	11	14	5	0
1+	4	5	4	9	1
0	5	4	7	11	24

TABLE II.

Degree of Reaction	Concentration in mg. per c.c.				
	50	25	10	5	1
4+	1	0	0	0	0
3+	5	2	0	0	0
2+	12	12	7	1	0
1+	2	6	9	4	0
0	3	3	7	18	23

TABLE III.

Degree of Reaction	Concentration in mg. per c.c.				
	50	25	10	5	1
4+	0	0	0	0	0
3+	0	0	0	0	0
2+	0	0	0	0	0
1+	2	1	1	0	0
0	23	24	24	25	25

SKIN TESTS ON CONTROLS

Intradermal tests were done on twenty-five patients with thiamine hydrochloride solution in which chlorobutanol was used as a preservative. The number of cases showing the degree of reaction with each dilution are shown in Table I.

Intradermal tests were done on twenty-three cases with a solution of thiamine hydrochloride in physiological saline. The results are shown in Table II.

Scratch tests using a solution of thiamine hydrochloride in physiological saline were done on twenty-five additional cases. The results appear in Table III.

INTERPRETATION OF SKIN TESTS

Comparison of the intradermal skin reactions in the case reported with those of the control groups (Tables I and II) indicates that dilutions of 50 mg. per c.c. and 25 mg. per c.c. are not reliable in testing for thiamine sensitivity. When dilutions of 10 mg. per c.c. and 5 mg. per c.c. are used, pseudopods and wheals are probably indicative of a sensitivity to the vitamin. In a dilution of 1 mg. per c.c. any reaction greater than the saline control should be considered significant, especially when a solution of thiamine hydrochloride without preservative is used.

Comparison of the scratch reactions in the case reported with those of the control group (Table III) indicates that pseudopods, wheals or flares greater than 1 cm. are indicative of thiamine sensitivity. This method of testing should be used in preference to the intradermal test when sensitivity to thiamine is suspected.

The value of a positive intradermal test with thiamine hydrochloride has been questioned. Kalz[2] found that all of thirty patients tested with a concentration of 10 mg. per c.c. developed an urticarial wheal. He concluded that skin tests with thiamine hydrochloride were not of diagnostic importance. Stiles[11] suggested that solutions of no greater concentration than 5 mg. per c.c. should be used for testing.

Previous reports describe two types of reactions to thiamine hydrochloride. The first is likened to the thyrotoxic state,[4,5,12] and is characterized by rapid pulse, irritability, insomnia, weakness, and trembling. The second appears to be allergic[1,3,4,10] and is characterized by itching of the skin and eyes, sneezing, urticaria, dyspnea, wheezing respirations, tinnitus, and vomiting. Two cases of severe sudden collapse with recovery after epinepherine[8,9] and two cases of sudden death[6,7] have been reported after the administration of thiamine.

Most serious reactions have occurred after the prolonged parenteral administration of the drug, suggesting that the sensitivity had been recently acquired. One death was reported after the fourth injection. Most of the patients observed mild reactions during the course of thiamine therapy, such as a wheal at the site of injection, itching of the skin, sneezing, wheezing, cough, dyspnea, perspiration, tinnitus, and vomiting, prior to subsequent severe reactions. The time interval elapsing between the onset of treatment and the appearance of these symptoms has varied considerably.

SUMMARY

1. Sudden collapse followed an intramuscular injection of thiamine hydrochloride.

2. Positive intradermal and scratch tests were elicited on the patient and compared to seventy-three controls. Skin tests on the patient were completely negative fifteen months later.

3. Scratch tests are superior to intradermal tests in detecting thiamine sensitivity, for fewer false positive tests are obtained.

4. When an injection of thiamine is contemplated, the patient should be questioned concerning reactions from previous injections. In case of doubt, skin tests should be done.

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INTRACTABLE BRONCHIAL ASTHMA

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ATOPIC CATARACT

Report of a Case with Tabulated Summary of Previously Reported Cases

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THE association of certain diseases of the skin and cataracts has been known for a long time. As far back as 1868 Rothmund[38] described four cases occurring in related families. The skin condition consisted of telangiectasia appearing during the early months of life over the face, gluteal region and the extremities; bilateral cataracts appeared in these children between the fourth and sixth years. Subsequently, ten or eleven similar cases were described, the skin manifestations being called poikiloderma atrophicans vasculare. In 1904 Werner[49] described another type of skin lesion, scleroderma, associated with the development of lenticular opacities. In Werner's syndrome the skin changes appear between the twentieth and thirtieth years and consist of thickening and hardening with atrophy of the subcutaneous tissue and glands; the feet are most severely affected, the legs, forearms, hands and face to a lesser degree. A total of thirty odd cases of scleroderma complicated by bilateral cataracts has been reported. In addition to the appearance of bilateral cataracts, other characteristics are noted in Werner's syndrome and reflect the part probably played by endocrine disturbances. In most of the cases reported there was early whitening of the hair; in many there were a juvenile build, alteration in the voice and eunuchoid features in the males.

NEURODERMATITIS AND CATARACT

The skin lesions of both Rothmund's and Werner's syndromes are very different from the lesions of the skin disease known as disseminated neurodermatitis. Not only are the papular, lichenified, disseminated or confluent lesions of neurodermatitis different from the lesions exhibited in the uncommon poikiloderma and scleroderma syndromes, but the entire background of the disease is different. However, an association of severe, long-standing neurodermatitis with the development of unilateral or bilateral cataracts has also been shown to occur. The first such cases were reported in the German literature by Andogsky[2] of Russia, in 1914. Since that time a total of twenty-seven cases has been reported in Europe, one in Australia and thirty-three in the United States. In view of the fact that neurodermatitis is a common skin disorder, the occurrence of cataracts in patients with neurodermatitis is obviously uncommon. For that reason the present case is being presented.

It is generally agreed today that disseminated neurodermatitis, in part, at least, belongs to that group of diseases placed under the heading of atopy, the most significant characteristic of which is the hereditary influence on the transmission of a state of hypersensitivity. Sulzberger[42]

TABLE I. CASES PREVIOUSLY REPORTED IN THE AMERICAN LITERATURE

1 Author	2 Year Reported	3 Sex	4 Family History for Allergy	5 Age Dermatitis First Appeared	6 Age Cataract First Appeared	7 Interval Between 5 and 6	8 X-ray Therapy	9 Associated Allergies*	10 Per Cent Blood Eosin.	11 Skin Reactions* D	11 Skin Reactions* I	12 Cataracts*
Davis[15]	1921	F		2	15	13		A.		—		B
Daniel[14]	1935	F	+	1½	14½	13	+	Ur, R	15.5	+	+	B
		F	+	2 mos.	17	17	+	A.	25	+	+	U
		M	—	14	35	21	+	R, Ur	16	+		B
Sulzberger[40]	1936	M	+	Infancy	23	23	+	A, H.F.	8-12	+		B
Brunsting[5]	1936	F	+	6	16	10	+	H.F., R.		+		U
		M	—	Infancy	26	26	None	A,R, H.F., Ur		+		B
		M	+	Infancy	21	21	+	R.,H.F.	23	+		U
		M	—	Infancy	21	21	+	Ur		+		U
		F	?	12	23	11	None	M?				U
		F	—	31	Rt. 24? Left 33	27	+	A, R		+		B
		F	+	Infancy	Rt. 38 Left 33	?	+	H.F.				B
Mayo Clinic[5]		F										
		F										
		F										
		M										U
Cazort and Cook[11]	1938	F		7	15	8			4	+	+	B
Beetham[3]	1940	F	+	Infancy	27	27	+	H.F., A	5	+		B
		F	—	16	17	1		A	4-14	—		B
		F	+	Infancy	17	17		None				B
		F	+	2	17	15		None				B
		M	—	Infancy	17	17		None	10	—		B
		F	+	20	31	11		A		—		U
		M	+	15	29	14		A		+		U
		M	+	Infancy	Infancy	0		None				B
		M	+	6 mos.	14	13		H. F.		+		B
		M	—	Infancy	25	25		A				B
McDannald[29]	1943	M	?	5	18	13		A		+		B
		F	—	13	16-17	3	+	A		+		B
Cordes and Cordero-Moreno[13]	1946	M	+	6 mos.	15	14		A	11	+		B
		M	?	5	31	26						B
		M		47	49	2				+		B
		F		3	17	14		A, H.F.		+		B

* A = Asthma
H.F. = Hay Fever
R = Rhinitis
M = Migraine
Ur = Urticaria
D = Direct Testing
I = Indirect Testing
B = Bilateral Cataracts
U = Unilateral Cataracts

states that there is "strong presumptive evidence in favor of the important role of specific hypersensitivity in the production of all stages of atopic dermatitis." It should be pointed out that Sulzberger employs the term atopic dermatitis to include neurodermatitis. Sulzberger, Spain, Sammis and Shahon[43] state: "The above-mentioned results aid in establishing the picture of neurodermatitis disseminatus as an atopic disease of the most classical type, often with a surprisingly high degree of polyvalent hypersensitiveness." Many allergists[16,44] concur in this point of view.

In addition to vascular structures (which may represent the common anatomic denominator in most allergic reactions, including those of atopy), there are three tissues in which the disturbed physiology of allergy may take place. These are the skin, mucous membranes and, as some believe, smooth muscle. In the type of case being presented, another tissue is possibly the site of allergic reaction. This is the crystalline lens. The anlage of the human lens can be seen in embryos of 4 mm. as a thickening of ectodermal cells overlying the optic vesicle in the region of the forebrain. The lens, like the skin, therefore, is ectodermal in origin. It

TABLE II. CASES PREVIOUSLY REPORTED IN THE EUROPEAN AND AUSTRALIAN LITERATURES

Author	Year Reported	Age	Sex	Skin Lesion	Age at Onset of Skin Lesion	Age at Onset of Cataract	Cataract*
Andogsky[3]	1914	27	M	Prurigo	3	25	B
		24	F	Eczema	10	22½	B
		25	M	Eczema			B
Vogt[47]	1922	28	M	Neurodermatitis	Early Youth	27	B
Kruz[26]	1924	22	F	Eczema			B
Lowenstein[25, 27]	1924	34	M	Neurodermatitis			B
		53	F	Neurodermatitis			B
	1926	18	F	Eczema	8		B
Siegrist[39]	1928	18	F	Neurodermatitis	17	18	B
Ollendorf[32] and Levy	1932	23	M	Eczema	6	22	B
Oltmanns[33]	1932	23	M	Prurigo	8	23	B
		46	M	Prurigo	39	39	B
Metzger[30]	1932		M	Neurodermatitis	Early Youth		B
			M	Neurodermatitis	Early Youth		B
			M	Neurodermatitis	Early Youth		B
			F	Neurodermatitis			B
Laszlo[22]	1933	20	M	Prurigo	7	19½	B
Adler[1]	1933	26	M	Neurodermatitis	Childhood	25	B?
Gault [18]	1933	32	M	Neurodermatitis	20	22	B
Kugelberg[21]	1934	15	M	Ichthyosis and Neurodermatitis	6 months	15	B
		27	M	Eczema	5	25	B
Sannicandro[39]	1936	40	F	Neurodermatitis			B
Rollin[37]	1937	31	M	Neurodermatitis	22	29	B
		30	F	Eczema	Childhood	29	B
Tostevin[45]	1938	21	M	Neurodermatitis	Infancy	21	B
Milner[31]	1941	26	M	Eczema	Many years duration		B
Cibis[13]	1942	41	F	Eczema	4-5 weeks	36	B
		46	M	Eczema	10	39	B

*B—Bilateral

would seem not far fetched to believe that where the skin has been the seat of prolonged, extensive and severe hypersensitivity, an organ allied to it embryologically might ultimately come to participate in the hypersensitive process. This is an idea which has been expressed repeatedly by those who have observed the association of neurodermatitis with cataract. This association constitutes the basis for describing this type of cataract as atopic, though there is additional, more concrete evidence to support that description.

REVIEW OF FORMER CASES REPORTED

Table I lists all the cases of neurodermatitis associated with cataract that have been reported in the American literature to date. Table II lists the cases reported in the European and Australian literatures.

The cases are grouped separately because the data presented in the European literature are lacking in much of the detail, especially from the point of view of allergic interpretation, offered by the American reporters. Table I shows that the family history for allergy is positive in most instances, that many of the patients have allied allergies, that almost all the patients are in the adolescent or early post-adolescent stage when cataract develops, that in the few instances where blood eosinophile counts are mentioned, the count is 4 per cent more (in several cases being considerably higher than is found commonly in the allergic state), and that skin tests, where done, are usually positive. In the few cases where passive transfers were done, the presence of reagins in the blood of the

patient is demonstrated by positive reactions in the sensitized sites of the substitute.

The two most striking features in the development of atopic cataracts are (1) the long interval that intervenes between the first appearance of the skin lesion and the appearance of the opacity and (2) the speed with which the cataract matures once it comes on. Once the cataract begins to develop, it may mature completely in a few weeks. The changes occurring in the lens are irreversible.

There are several arguments which may be offered to refute the possible allergic nature of the cataract complicating neurodermatitis. Most of them can be adequately met. It may be asked, for example, why the associated cataract appears so infrequently if neurodermatitis as a manifestation of allergy occurs so commonly. It will be noted from column 7 of Table I that the interval between the first appearance of the skin lesion and the development of the cataract is a long one, being on the average, fifteen years. This means that the dermatitis must be of approximately fifteen years' duration, continuously or intermittently, before the lens is sufficiently traumatized allergically (i.e., sensitized) for the cataract to develop. In the majority of cases, atopic dermatitis does not last that long; the lesion clears up spontaneously or its disappearance is hastened by medical management long before fifteen years elapse. Again, it may be asked why the cataract is not invariably bilateral. Actually it is not the invariable finding in allergy to have the disturbance universal in its distribution. Thus, in chronic recurrent urticaria, though the lesions may be spread diffusely over the body, there may still be large areas of skin uninvolved. In perennial vasomotor rhinitis one occasionally sees only one side of the nose affected. Most classically, in migraine only one side of the head is often involved in an attack, and that, commonly, the same side in each attack. It is quite possible, too, that if the cases with unilateral involvement were followed a little longer, the other eye might have been found to have become involved. The objection that has been most often raised against the belief that this type of cataract in young people is atopic, is the fact that many of the patients concerned have received x-ray therapy for their chronically inflamed skin. It is known that x-rays can produce degenerative changes in many tissues, including the crystalline lens. That x-ray therapy in the cases with which we are dealing is not the cause of the cataract is supported by two considerations: (1) there are cases in which x-rays had never been used; (2) in acne vulgaris, a skin disease much more common than neurodermatitis and for which x-ray is frequently employed, cataract is not seen. This fact has been pointed out by others.

Among the factors which have at times been implicated in the causation of this type of cataract, one may mention dietary deficiencies, endocrine dysfunction and disturbances in the nervous system. Beetham[3] found his patients undernourished and underweight; eight of his ten

cases averaged 20 per cent underweight. Goeckerman in discussing Brunsting's[5] paper also emphasizes the inadequate nutrition of patients with atopic dermatitis. Other writers who have reported cases of cataract associated with neurodermatitis have not stressed this point. Beetham[3] himself states that although cataracts and dermatitis can be produced experimentally in animals by vitamin deficient diets, such causal relation has not been proved for humans. The part played by endocrines is uncertain. In Werner's syndrome the abnormality in build, the change in voice, the early whitening of the hair and the eunuchoid features in males point to dysfunction of the endocrine system. In cataract with neurodermatitis the evidence is much less suggestive. Bellows[4] points to the histologic similarity to cataracts of known endocrine origin, the youth of the patients, the rapid maturation and the commonly bilateral involvement as indicating a possible endocrine causation. However, several of these factors are also common in allergy. Investigations from the chemical and clinical points of view do not support the endocrine explanation. The German literature, particularly, emphasizes the probability that malfunction of the endocrines is responsible for the formation of the cataract. Very little evidence is offered to justify that contention. Least of all can the autonomic nervous system be directly implicated, notwithstanding the well-recognized irritability of many patients with long-standing pruritic lesions.

Of the total of sixty-one cases reported to date, thirty-five were males and twenty-six were females; fifty had bilateral cataracts, seven had unilateral cataracts, and in four the distribution is not mentioned. All the European cases had bilateral cataracts; the average age at which cataract developed among them, where the age is given, was twenty-five years. The data are too meager for calculating the interval between the first appearance of the skin lesion and the appearance of the cataracts in the European cases. The average age at which the cataract appeared among the American cases was twenty-two years, and the average interval between the very first onset of the skin lesion and the appearance of cataract was fifteen years.

THEORIES OF THE MECHANISM OF ATOPIC CATARACT FORMATION

In seeking an explanation for the mechanism whereby the atopic cataract is formed, Daniel[14] in 1935 stated: "A fine change in function of these epithelial cells of the ciliary body, in the content of the aqueous fluid or in the level of permeability and selectivity of the capsule of the lens can readily be reasoned to interfere with the efficient metabolism of the lens and its transparency, thereby producing a cataract in an otherwise normal eye." Woods,[14] in discussing this suggestion, criticized the assumption that the cells of the ciliary body might be involved and that there was a change in the contents of the aqueous. Nor was Woods,[14] a pioneer in the work on the chemistry and immunology of lens proteins,

too ready to accept the hypothesis that a change in the permeability of the lens capsule, resulting from the participation of the lens in the allergic process, allowed passage of elements from the normal aqueous through the altered capsule, causing precipitation of lens protein. Beetham[3] removed aqueous from the eyes of two of his reported patients and did intradermal tests with this material on the same patients. The reactions were negative. Since anything reaching the lens would have to be present in the aqueous the assumption that there was an exciting antigen in the aqueous might make one expect a positive skin reaction with aqueous. If a nonantigenic yet traumatizing constituent of the aqueous passed through the capsule, a positive skin reaction would not take place, but as will be pointed out later, the evidence does not indicate that the permeability of a cataractous lens differs from that of a normal lens. Nor has it been demonstrated conclusively in other manifestations of allergy, in spite of occasional, uncritical reports to the contrary, that the human can be sensitized to the *normal* products of his own secretion. Brunsting did a skin test on one of his affected patients, using this patient's own lens material as the test substance. The reaction was negative.

IMMUNOLOGY OF LENS PROTEIN

The current status of the immunology of lens protein is presented in excellent summary by Bellows.[4] The literature on the immunology of lens protein was conflicting, some investigators reporting sensitization of animals to their own lens substance and others stating their failure to effect this, until the work of Woods and Burky[51,52] was reported, beginning in 1927. The experimental results of these men supported Uhlenhuth's[46] original observation that lens protein is organ specific and not species specific. They were also able to corroborate and extend the findings of Mörner[32] who had identified alpha and beta crystallins in whole lens. Burky and Woods[8] have shown that lens protein is complex and consists of at least three different proteins excluding the capsule. These proteins—alpha, beta, and gamma crystallins—are chemically and immunologically distinct. The alpha fraction is the most active antigenically and is regarded by Woods, Burky and Woodhall[53] as the true organ specific substance of whole lens, for only that fraction can act as an antigen in the homologous animal. When the alpha fraction is combined with the other fractions, as in the whole lens, it is not antigenic in the homologous animal because the inert beta and gamma crystallins inhibit the action of the alpha fraction. Beta and gamma crystallins are inert in homologous species. Woods and Burky[52] state that there is little evidence that lens protein from an unruptured capsule exerts any antigenic activity. After rupture of the capsule some individuals develop cutaneous sensitivity to lens protein, their own lens serving as the sensitizing antigen. This may help to explain what occurs in phacoanaphylactic endophthalmitis following surgery for cataract in some instances.

In 1922 Verhoeff and Lemoine[47] ascribed to allergy the ocular inflammatory reaction occasionally set up postoperatively following cataract extraction, stating that the residual injured lens protein served as the exciting antigen. On the basis of the experimental facts supplied by Woods and Burky,[51,52] it has been reasoned that a loss or disappearance of beta gamma crystallins as the result of incision into the capsule releases the antigenic alpha fraction from its inhibition so that it becomes active. Burky[6] has also demonstrated that antigenicity of lens substance can be enhanced by staphylococcus toxin for he was able to produce cutaneous sensitivity to lens substance in rabbits by repeated and coincident injections of staphylococcus toxin and lens substance and, subsequently, by needling the eyes of such sensitive rabbits, produce the clinical and histologic picture of phacoanaphylactic endophthalmitis as seen in man.

Normally, and usually even after injury to the lens capsule, a positive skin reaction with lens substance is not obtained because active alpha crystallin within the subject's lens, being inhibited by the beta-gamma fractions, has been unable to sensitize the subject. If the inhibiting elements are lost or are present only in small amounts as the result of surgical intervention or otherwise, the antigenicity of the alpha fraction may become operative and thus sensitize the individual. If the individual is sensitive to lens protein because of such imbalance of fractions, he may give a positive skin test, and ocular reactions may follow capsulotomy. If the individual is not sensitive to start with, he may be rendered sensitive after capsulotomy so that an allergic inflammatory change may ensue after injury to the second lens. Burky and Woods[9] found eleven out of sixty-four patients with cataract gave a positive skin reaction to lens substance and found no positives among seventy-five normals. It is not difficult to understand the negative skin reaction obtained by Brunsting[5] on the one cataractous patient on whom the test was done.

LENTICULAR CAPSULE

The lenticular capsule is a semi-permeable membrane which allows the passage of all electrolytes—water, salts, and other crystalloids—and also small and medium-sized colloidal particles. It is through the capsule that substances reaching or leaving the lens must pass. Nutrition and elimination are effected through the aqueous which is formed by the ciliary body. The lens has no circulation of its own. Physiologically, transparency of the lens is dependent upon the maintenance of capsular permeability. The capsule may exhibit considerable fluctuation in permeability depending upon changes in its environment. However, it has not been established definitely that the permeability of a cataractous lens differs from that of a normal lens. Thus Gifford, Lebensohn and Puntenny[19] found the permeability of the capsule in five cataractuous lenses from human beings was approximately the same as that of normal rabbit lenses. The original theory of Löwenstein,[26] that capsular permeability

increases with age so that senile cataract might be regarded as a product of the more ready passage of toxic substances into the lens or the loss of nutritive elements from the lens, is not substantiated by the later experimental findings of Friedenwald[17] and others. Friedenwald has shown that the permeability of lens capsules from young animals is greater than that of the lens capsules from adult animals. Variations in osmotic pressure and hydrogen ion concentration have been ineffective in producing cataract *in vitro*. In mature naphthalene cataract, Gifford, Lebensohn and Puntenny[19] were able to find no increase in the permeability of the capsule. Furthermore, Woods and Burky[52] have pointed out that the available evidence indicates that the fully developed lens capsule is impermeable to antibodies.

Bearing all these fundamental facts in mind, one cannot at this time postulate a change in capsular permeability to the contents of the aqueous as the immediate physical cause for the cataract formation in the entity under discussion.

CASE REPORT

The case herein reported is that of a girl, seventeen years old, who was seen for the first time on May 13, 1946. She was referred by her family physician because of an extensive rash over her face, neck, elbows and behind her knees. The patient's paternal grandmother had asthma and a paternal aunt had hay fever. At the age of two, a rash had appeared over the face, elbows and popliteal spaces of the patient. The rash over the elbows and knees would come and go and thus been intermittently present for the last fifteen years, being worse during the winter. The rash over the face initially lasted a few weeks or months, disappeared, appeared again when the patient was three years old, again lasting a few months, and then did not recur until the patient began to menstruate at about thirteen years of age. The rash at this time involved the neck and chin and only slowly came to cover the face, so that it was not until she was fifteen that the whole face became involved.

The rash had always been itchy and had been responsible for much scratching. During the past four years the rash had been worse just before the menses. From February, 1944, to May, 1944, when the patient was fifteen, she was given x-ray therapy on three occasions to the face, neck and cubitals for a total of 60 roentgens. In February, 1945, as the result of a routine school examination, the patient consulted an optometrist who found that her visual acuity for distant vision was 20/30 in the right eye and 20/20 in the left eye. In September, 1945, her vision was again tested and was again found to be 20/30 in the right eye and 20/20 in the left.

At the age of six the patient had had pneumonia, and at the age of eight a tonsillectomy and adenoidectomy had been done. There was no other significant past medical history.

On April 11, 1946, the patient noted that the glands of the neck and those behind the ears were swelling. The following day her temperature rose to 103° and small blisters appeared on the chin and around the mouth. These blisters ruptured and became crusted. About one week after the glands in the neck were observed, the scalp became extensively covered with large pustules which attained the size of marbles, ruptured, oozed and crusted. Numerous such lesions appeared throughout the scalp. From April 12, 1946, to May 5, 1946, the temperature fluctuated between 100° and 103°, but the patient did not feel very ill. The tempera-

ture returned to normal on May 5 and remained so. During this period of three weeks she was seen several times by her family physician. The only medication taken by the patient was calcium salts.

When the patient was seen on May 13 she did not appear acutely ill. The temperature was 98°, pulse 80, blood pressure 96/60, weight 112 pounds. The scalp was diffusely covered with large numbers of heavy crusts up to 1 centimeter in diameter; many of them were elevated several millimeters. No fresh pustules were seen. Many crusted scales were trapped in strands of hair. About half way down along the anterior margin of the left sternocleidomastoid muscle there was a mass of matted glands. Individual nontender glands were easily palpable on the right side of the neck, over the posterior surface of the neck and behind both ears. The face was covered with small excoriated papules; the skin of the neck was thick, rough and deep brown in color. The skin over the flexures of the elbows and knees presented the characteristic lichenfied appearance of longstanding neurodermatitis. A silvery white opacity was noted in the left eye. This was a mature cataract. The right lens showed linear striae composed of punctate opacities in the anterior cortex producing the effect of wheel spokes. This was an incipient cataract. Visual acuity in the right eye was 20/30. With the left eye the patient could not recognize moving fingers at a distance of a few inches; she did, however, have perception of light. The fundus of the right eye was normal. Tension in both eyes was normal. Until the time of the examination the patient was not aware that she was blind in the left eye. The hairs of the eyebrows were broken and stubby due to the constant rubbing to overcome the itching. The rest of the examination was not significant.

The Wassermann test and urinalysis were negative, as was an x-ray of the chest taken the end of May, 1946. The white blood count on May 16 was 10,500 with 4 per cent eosinophiles; the remainder of the differential was normal. On May 20 a second blood smear showed an eosinophilia of 5 per cent. Direct intradermal skin testing on what appeared to be relatively normal skin of the arms gave slight to moderate reactions to practically all seventy food and inhalant extracts employed. Indirect testing (passive transfer) was therefore done. Indirect testing confirmed many of the direct tests. Reactions to the following substances were passively transferred: cottonseed, cow epithelium, dust, feathers, horse epithelium, horse serum, kapok, orris root, rabbit epithelium, silk, wool, timothy pollen (0.1 mg. N per c.c.), plantain pollen (0.1 mg. N per c.c.), tree pollens (0.1 mg. N per c.c.), cherry, grapefruit, orange, peach, strawberry, cinnamon, ginger, mustard, gum chicle, corn, rye, egg white, lamb, herring, oyster, salmon, chocolate, milk, almond, asparagus, celery, green peas, lima beans, sweet potato, and tomato.

The patient was operated upon on August 3, 1946. A combined extracapsular extraction of the left lens was done. The patient made an uneventful recovery. On September 3, 1946, vision in the right eye was 20/30 and in the left eye the patient had light perception correctible to 20/70 by means of a plus 11 sphere combined with a .50 cylinder, axis 40°. Both fundi were normal and the tension in both eyes was normal.

One of the striking results of skin testing in the former reports where skin testing was done is that though there were positive reactions to many foods and inhalants, silk among the inhalants and egg among the foods occurred most commonly. Reactions to these two substances were positive in the above case, both on direct and indirect testing.

During the three weeks that the patient was under observation, the lesions in the scalp continued to diminish, so that by June 3 the scalp was almost clear. The glands in the neck also had entirely disappeared during this time. The most im-

pressive feature of the patient's course, however, was the improvement that took place in her old skin lesions. The skin of the face, neck, elbows and knees became much smoother, softer and more pliable, a change that may be attributed in part most likely to the elevated temperature experienced by the patient over a period of about three weeks. In smaller part the improvement may have fitted in with the history that the lesions were always better with the onset of warm weather. One must, of course, remember that marked fluctuation in the severity of neurodermatitis is a very common occurrence. The nature of the pyodermia of the scalp is not known. None of the drugs known to cause cataract was used by the patient before her acute illness or during it. The general consitutional diseases such as diabetes and nephritis occasionally causing cataract were excluded as possible causes.

The prognosis in cataract associated with neurodermatitis is good if surgery is skillfully effected. Postoperatively vision in the affected eye or eyes is usually restored by means of correcting lenses.

SUMMARY

A case of neurodermatitis of fifteen years' duration in a girl of seventeen in whom bilateral cataracts developed, one reaching maturity in a period probably not exceeding seven months at most, is presented. The case fits into an entity previously described by a number of observers in both the European and American literatures. There is evidence to believe that the cause fundamentally responsible for the long-standing neurodermatitis is also responsible for the formation of the cataract and that atopy is probably involved in both. The mechanism whereby the cataract is produced is not known. The available experimental evidence does not at this time support the contention that altered permeability of the lenticular capsule is the immediate mechanism by which the opacity is formed.

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(Continued on Page 396)

THE SIGNIFICANCE OF CHRONIC BRONCHITIS IN INFECTIOUS BRONCHIAL ASTHMA

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THE capacity of sulfonamides and antibiotics to eradicate acute pulmonary infections of various types has given new hope for a causal therapy of chronic bronchitis. Encouraging results from prolonged administration of penicillin as aerosol[8,17,47] indicate that the transition from certain acute to chronic bronchopulmonary infections may be avoided. Thus, the incessant pleas for prevention of chronic bronchitis and bronchiectasis by early elimination of pulmonary infections, may find, at least, their realization.

The recognition of developing nontuberculous infections in the lower respiratory system is still a challenge to the medical profession. The frequent failure of early diagnosis is due mainly to misleading symptoms and associated conditions. Upper respiratory infection is frequently present in patients with chronic bronchitis, and is usually held to be the primary cause. Most confusing are asthmatic manifestations which are commonly interpreted as true bronchial asthma, the existing pulmonary infection being considered as secondary to an allergic condition.

In the course of treating respiratory infections with penicillin aerosol, the author has been impressed by the improvement or disappearance of asthmatic symptoms in many cases which had been considered as bronchial asthma.[17] As a rule, these patients were children or young adults; although in some of them the condition had existed for several years, none of those who recovered had evidence of gross pathological changes such as bronchiectasis. In all of these asthmatic patients the disease had been initiated by an acute, severe respiratory infection.

Observations of this kind emphasize the importance of proper and early evaluation of etiological factors in infectious asthma. Most publications on this subject do not consider adequately the significance of acute respiratory episodes in the beginning of this type of asthma, and do not seem to realize the implications for a rational therapy of this serious disease. In view of this, the following study attempts to establish the actual role of bronchopulmonary infection in the picture of infectious asthma from the onset to its end.

In recent years, it has been realized that asthma is not always due to allergy but that it may be also a symptom in other conditions without allergic background. The postulate of ten years ago that "who wheezes has asthma" as a manifestation of allergy,[51] has been replaced by the warning "all is not allergy that wheezes." It is now generally acknowl-

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edged that cardiac conditions can produce asthmatoid respiration, and that asthma occurring in silicosis, tuberculosis and pulmonary malignancy should be considered apart from true bronchial asthma.[49] The same stand has not been taken, so far, in nonspecific pulmonary infections with asthmatic symptoms. Although chronic bronchitis and bronchiectasis are known to produce asthma without the presence of allergy,[2,9,37,55,60] this type of asthma is usually not differentiated sufficiently from bronchial asthma.

Occasional publications, older as well as recent ones, did stress the close relationship between pulmonary infection and asthma. Ever since clinicians of the nineteenth century had observed that certain acute respiratory episodes could be held responsible for the "humid asthma of practitioners with chronic mucous catarrh" (Laennec)[4,19,31,44], numerous studies have confirmed pertussis, measles, pneumonia and influenza as likely causes in many cases of asthma.[6,7,22,26,38,43,46] The significance of unresolved pulmonary infiltrations in the history of some of these patients has been repeatedly emphasized.[22,38] Moreover, the dominant feature in a high percentage of cases diagnosed as bronchial asthma appeared to be chronic bronchitis.[21,28,32]

Although these factors point toward infection as the primary etiology of infectious asthma, the tendency to interpret this condition as an allergic manifestation still prevails, and seems even to gain ground.[15,57] A history of eczema or pollinosis in a patient with the infectious type of asthma is regarded, *a priori,* as evidence of its allergic etiology. In absence of the usual type of allergy, the presence of eosinophilia in the patient's blood and of allergy in his family suffice for the assumption that hypersensitivity has been responsible for the asthmatic condition.[11] Respiratory infections, *per se,* are not believed to cause asthma in any individual. It is assumed that these infections sensitize an allergic or potentially allergic individual to bacterial and other proteins, thereby producing asthma by virtue of an immunological mechanism. Pneumonia and other respiratory episodes are considered to be forerunners of true bronchial asthma in patients with allergic background only,[57] and irreversible lesions in chronic asthma are attributed to longstanding allergy of some kind.[10,56] Thus, bronchitis, bronchopneumonia and bronchiectasis, if associated with asthmatic manifestations and one or another of the findings allegedly indicative of allergy, are thought to be initiated by allergic reactions.[35,54,61,62] Consequently, early desensitization has been advocated in allergic and possible allergic children after their being affected by respiratory infections in order to protect them from developing bronchial asthma.[38,57]

This conception of allergy in infectious asthma is not satisfactory from a clinical point of view; it does not illuminate certain features of this condition, and it tends to obscure the distinction of chronic bronchitis from bronchial asthma. The existing confusion in this respect is best reflected

in the various classifications of bronchial asthma in which intrinsic asthma, chronic asthma, asthmatic bronchitis, and infectious or bacterial asthma are terms applied to conditions which are, rather arbitrarily, assigned to allergy, to infection and to both.

It was believed that an investigation of cases grouped as infectious asthma might answer the question whether this disease should be considered as mainly due to infection or to allergy. As mentioned before, this problem appears of major importance with regard to proper management of infectious asthma in its early stage.

The basic material for this study was a series of 235 records of patients who had been hospitalized at the Genesee Hospital between 1935 and 1945 with the diagnosis of bronchial asthma. From these cases, in which no patient with heart disease, silicosis, tuberculosis, and the like was included, 100 with infectious asthma were selected for further investigation. The selection was made in accordance with a recent classification of asthma[16] in which essential characteristics of infectious asthma are: an acute respiratory infection which initiates the condition, and respiratory infection dominating the picture through its course. Using the same classification, patients with infectious asthma and coexisting allergic manifestations are designated as mixed atopic and infectious asthma. They are also included in this series.

In all 100 of these asthma cases, a severe respiratory infection was assigned by the patient or by relatives as its cause. Moreover, the course of events, traced meticulously, proved that this infection had initiated a respiratory disease, with asthmatic manifestations following sooner or later.

In forty-four of the 100 patients, the onset could be directly related to a specific illness; namely, pertussis in thirteen, pneumonia in seventeen, and influenza in fourteen cases. In the remaining fifty-six, less specifically diagnosed infections, such as bronchitis, bad chest cold, grippe, et cetera, were found to have initiated the asthmatic condition. It was inferred from the records of many patients that infections diagnosed as pneumonia and chest colds had in reality been pneumonitis of the non-pneumococcal type. Frequent occurrence of pneumonia in early childhood, occasional designation as unresolved pneumonia, and recurrence of a severe "grippe," spoke definitely for that type of subacute pulmonary lesions which may follow measles, influenza and the like. Of fourteen patients where influenza could be held responsible for the infectious asthma, eleven were sufferers from the epidemic type occurring during the first World War.

The age groups, in which the patients with infectious asthma had been hospitalized during the past ten years, can be noted in Table I. The age groups in which these patients had contracted one or the other of the initiating infections can be seen in Table II.

It becomes obvious from Tables I and II that a little more than half of all cases with infectious asthma had been hospitalized at an average age

TABLE I. AGE AT TIME OF HOSPITALIZATION

Age Group	*Number of Cases*
Under 10 years	16
10-20	3
20-40	28
Over 40	53

TABLE II. AGE AT ONSET OF INITIATING INFECTION

Age Group	*Number of Cases*
Under 10 years	31
10-20	6
20-40	33
Over 40	30

of over forty, but that in 70 per cent of the whole group the actual onset of the disease occurred before the age of forty. The average age of onset of infectious asthma in this series was 22.3 years.

In ten of the thirty-one patients in whom infectious asthma had its onset in the first decade of life, pertussis was the assigned cause, and in six more, pneumonia. Among the thirty-three patients in whom asthma originated at the age of twenty to forty years, there were ten who developed this condition following influenza.

Of eight patients who died in the hospital during the past ten years from infectious asthma, four were under the age of forty years and four beyond that age at the time of death. However, in five of the eight deaths, the onset of infectious asthma occurred before the age of ten, and in only one after forty.

Allergy in some form had existed or was suspected in twenty-two patients. In sixteen, clinical allergy had been present. In eight of these sixteen patients, the allergic manifestations were of the usual type, such as pollinosis and eczema. In seven others, hypersensitivity to aspirin alone existed, and in one patient both pollinosis and aspirin hypersensitivity could be found. In thirty-eight patients skin tests were done; nine showed definitely positive skin reactions. In five more patients, the result was considered as questionable.

In twenty-eight patients the family history revealed the presence of atopy or of possible atopy in one or more relatives. The eosinophil count was normal in most cases with coexisting allergic manifestations, as it was in the great majority of this group. In some patients without any evidence of hypersensitivity, excessive eosinophilia was present.

The relationship between previous or present allergy and the asthmatic condition was held to be of great significance in this series. The asthma of the eight aspirin-sensitive patients was of an especially severe character. However, it was different from the infectious asthma, taken as a whole, only inasmuch as salycilates, frequently also codeine and morphine, aggravated the existing asthmatic condition. Two of the eight aspirin-sensitive patients died in the hospital. Among the eight patients, who at some time had presented common allergic manifestations, were three who developed pollinosis several years after a chronic bronchopulmonary infection had become evident. Two had been diagnosed as bronchial asthma only after hay fever had appeared. In the remaining five patients, allergic conditions preceded infectious asthma; in two cases, intervals of six years and eighteen years, without respiratory symptoms, had elapsed

before infectious asthma developed. Three patients had suffered from seasonal allergic rhinitis and asthma shortly before, or at the time of, infectious asthma. In all five with preceding or present allergy, a respiratory infection of severe character occurred before the appearance of infectious asthma.

The most striking feature in all patients with infectious asthma was the clinical evidence of a gradually progressing infection of the bronchopulmonary system. The sequence of events is best demonstrated in the records of patients who had been observed over many years. Tonsillectomies had been performed in children with periodic respiratory episodes following pertussis or bronchopneumonia. Not infrequently, patients had been under observation for tuberculosis in clinics and sanatoriums. Months or even years after the acute respiratory infection, the progressing condition had been diagnosed as bronchial asthma, asthmatic bronchitis, or intrinsic asthma. Asthmatic paroxysms with free intervals, although present, did not dominate the picture. Persistent cough with purulent, at times malodorous or bloody sputum, indicative of suppurative and destructive changes, was the most troublesome symptom. Variations in the picture were, as a rule, due to the extent of the underlying pulmonary changes. The majority of patients were admitted during one or more acute exacerbations. Consolidations in the lungs were frequently present during these acute febrile episodes, usually diagnosed as pneumonia. In recent years, atypical pneumonia was noted as the diagnosis in a number of patients. Staphylococci and streptococci were usually predominant in the sputum of these patients. Unlike lobar pneumonia, the onset and termination of the pulmonary lesion was gradual. Frequently, there was evidence of previous damage of the respiratory system, and the new exacerbation left its marks in the affected lung.

Thirty-nine among forty-six patients, of whom roentgenograms had been taken, showed definite, and often extensive, pathologic lesions such as marked basal fibrosis with pleural involvement and atelectasis. Emphysema, chiefly of the patchy, compensatory type, was the rule. In two cases, one case a pneumothorax, and the other massive collapse of a lung, large emphysematous blebs were found.

Lipiodol studies were done on eight patients. Five presented bronchographic evidence of bronchiectasis, although many more patients had symptoms usually held characteristic of this condition.

The severity of the existing pulmonary lesions was not necessarily related to the duration of the disease. In twenty patients, who dated the onset of the asthma at least ten years earlier, a relatively mild course and the absence of marked gross lesions could be observed. On the other hand, eight patients with duration of their illness from two to five years presented extensive pulmonary changes. It seemed that the seriousness of the preceding acute illness had a major bearing on the course and the

clinical picture. Among eight roentgenograms taken of patients whose asthma began following influenza, seven showed extensive damage of the lungs. In nine others taken of those who developed asthma after pertussis, six revealed the same type of changes, indicating a severe, chronic, nonspecific bronchopulmonary infection.

Purulent lesions of the nose and sinuses were present in thirty-four patients. In at least half of these, the upper respiratory infection had occurred simultaneously with, or following, the appearance of lower tract respiratory infection.

The response to therapeutic measures of any kind, in all cases which could be followed, was, at best, temporary. This is also demonstrated by the periodic admissions of a great number of patients. Their conditions could generally be found to have become worse with every new acute exacerbation. Neither surgical measures on nose and throat, nor routine allergic and other treatments, although applied initially, prevented to an appreciable extent the progress of the disease.

Eight of the patients with infectious asthma died in the hospital during the ten-year period. The dominant feature at the time of their death was a chronic bronchopulmonary infection, as it had been during life. They died, as a rule, with clinical manifestations of asphyxia, and, not infrequently, with toxic symptoms. In three cases which came to autopsy, the anatomic findings in the lungs were essentially fibrotic-bronchiectatic lesions with suppuration in bronchi and fibrinous pleurisy. Two among the eight cases had evidence of possible allergy in the past, but in none was this present at the time of death.

In five of those eight patients who died, morphine was given before death. In at least three of them, the course of events was very suggestive of a close relationship between the administration of morphine and the death of the patients.

In one of the aspirin-sensitive patients, death was attributed directly to a dose of aspirin. Forty-five minutes after taking the drug he collapsed, and on the following day died, supposedly from anaphylactic shock. However, the life story, the clinical picture, and the anatomic findings of this patient were also characteristic of infectious asthma, without evidence of the usual type of allergy. His disease apparently began after an attack of influenza in 1918, and developed gradually to chronic bronchopulmonary infection with bronchiectatic-fibrotic lesions.

DISCUSSION

The study of one hundred cases of infectious asthma, in which a correlation of the characteristic features was attempted, indicates that the condition is fundamentally chronic bronchitis, with asthma as one of the many symptoms present. The etiological background of infectious asthma is a nonspecific chronic bronchopulmonary infection originating from

certain acute respiratory diseases. The same factors are involved in a great number of cases which are commonly labeled chronic bronchitis, with or without marked asthmatic symptoms.

Naturally, respiratory infection may have a different significance in certain patients with extrinsic and intrinsic asthma. However, in many, regardless of their being designated as asthmatic bronchitis, bronchial asthma, intrinsic or bacterial asthma, bacterial infection of the lower respiratory organs is undoubtedly the direct cause. They usually present all or most characteristics of infectious asthma if the necessary details have been investigated. Respiratory infection was the most conspicuous feature in the majority of Rackemann's cases with intrinsic asthma.[39,40]

The general belief that infection with bacterial allergy tends to take the place of the usual type of allergy with advancing age is not substantiated by actual figures from this study and from other investigations. In Rackemann's group of intrinsic asthma,[39] as well as in Unger's of chronic asthma,[57] the onset of the disease occurred in the majority under the age of forty, and in a rather high percentage in childhood. Observations, like Bivings'[5] and Taylor's,[52] on the frequent occurrence of a definitely infectious type of asthma in children, are confirmed by general experience. The surprisingly high incidence of chronic bronchopulmonary infection in young asthmatic soldiers, as found by Zoss,[63] speaks also against the assumption that chronic bronchitis is present chiefly as a complication in elderly patients with longstanding asthma.

The misconception that intrinsic asthma, apparently due to infection, is prevalent after the age of forty can be attributed to the fact that frequently there is a latency of several years between the onset of infection and the appearance of asthmatic symptoms. It is not unusual that a patient, whose asthma started in the later part of life, will admit after repeated questioning that he had been affected by "cigarette cough" for many years, or that he suffered since childhood from frequent colds which he "had a hard time to throw off." Usually, it can be elicited that an acute respiratory infection had initiated the respiratory symptoms.

Pertussis and bronchopneumonia, complicating measles and other infectious diseases, are known to be frequent, although not always appreciated, causes of chronic bronchitis and of bronchiectasis.[18,25,29,34,48] This explains why early childhood is a danger period also of infectious asthma. Later in life, influenza and severe pulmonary infections of similar character, not bound to a particular age, are important factors in the onset of this condition,[22,36] the nature of which in children is essentially the same as in adults.

The sequence of events usually begins with subacute pulmonary infiltrations following the acute respiratory infections, and leads frequently to that disease which has been studied for many years under various terms such as fibroid disease of the lung, chronic pulmonary catarrh, chronic pneumonia, chronic interstitial fibrosis, and the like.[33] Bronchi-

ectasis may or may not accompany the pyogenic process; if it occurs, it may develop early or may be found as an end stage after many years. It was in a child who had been affected by whooping cough, and in an old woman who had suffered most of her life from a chest ailment that Laennec demonstrated for the first time dilatation of the bronchi.

The causal relationship between acute initiating infection and the clinical picture of the asthmatic condition is more impressive in this series of selected patients with infectious asthma than in currently published groups comprising asthma of all types. It ought to be mentioned here that Peshkin[38] found all of the nonsensitive asthmatic children, in whom respiratory infection was the assigned cause, suffering from chronic bronchitis. Among patients diagnosed by Thomas and Taylor[54] as allergic bronchitis, almost half of the cases related their condition to pertussis, pneumonia and influenza, and in 14 per cent bronchiectasis was evident or suspected. Harkavy's[22] patients, whose asthma developed following unresolved pneumonia, belonged to the nonsensitive type.

It is justifiable to state that asthma, which develops after certain acute infections of the lower respiratory system, is entirely different from bronchial asthma due to allergy. The bronchopulmonary lesions in infectious asthma may and do cause asthmatic paroxysms which however are not related clinically to known allergens. Epinephrine does not act in infectious asthma as promptly as it does in an attack of allergic asthma. The pathologic changes in the former are mainly irreversible, whereas allergic reactions are, as a rule, transient in character. However, the favorable response to epinephrine of an asthmatic patient should not be evaluated as proof of an atopic background. Many cases with bronchitis and even with bronchiectasis, without evidence of allergy, may also experience great relief by epinephrine (Alexander[2]).

Therefore, pertussis and bronchopneumonia can hardly be considered as forerunners of true bronchial asthma. There are no actual observations available which substantiate the claim that bacterial infection may develop into an allergic condition. Allergic asthma and allergic rhinitis are frequently misinterpreted, in the beginning, as respiratory infections; thus the history of patients with true bronchial asthma may reveal "colds" and the like as precursor conditions. Diagnostic errors of this type do not justify the tendency to concentrate on the search for allergens in an asthmatic patient, thereby disregarding preceding respiratory infections.[57] A pneumonia, years before the onset of the asthma, may at times explain the situation more adequately than allergy or suspected allergy to dust and certain foods.

The conception of a transition from extrinsic to intrinsic asthma appears also rather academic. In the few patients of this series in which simple allergy seemed to develop into a different and more serious disease, the relationship between acute infection and the following infectious asthma

proved to be the same as in cases without allergy. Rackemann came to similar conclusions in his study of intrinsic asthma.[39]

Since common allergic manifestations occur rather frequently among the whole population, their presence in asthmatic patients does not necessarily explain the etiology of the asthma. Coexisting allergy in patients with heart disease, tuberculosis, and especially in those who suffer from chronic, nonspecific respiratory infections undoubtedly complicates the situation in theoretical and practical respects. A reflex mechanism or bacterial allergy may, in these cases, be of some significance for the asthmatic symptoms, although it has been emphasized that hypersensitivity to bacterial proteins can be held responsible for asthma of the infectious type, at best, in only rare instances.[23,45] In the majority of chronic asthmatic patients without evidence of allergy, the direct action of bacterial agents should be considered as the cause of the disease. Bacteria have the capacity to produce lesions with spasm and exudation in bronchial structures, factors from which obstruction of the air passages and asthmatic symptoms may develop.

The life history of patients with infectious asthma is, as a rule, of greater diagnostic help than the eosinophil count and positive skin tests without clinical relationship. The questionable significance of these laboratory tests has become more and more evident in recent years.[24,30,41,50]

The therapeutic failure in most cases of infectious asthma is explainable since none of the usual treatments is primarily directed against the original pulmonary infection. The attempt to influence, by desensitization, the immunological processes which might be involved in the development of chronic pyogenic lesions in the respiratory system is no more rational than was tuberculin treatment for tuberculosis, years ago. Elimination of existing nose and sinus infection, alone, should not be expected to cure infectious asthma, since this condition originates from infections which frequently involve upper and lower respiratory system simultaneously.[8,14]

All deaths from asthma in this hospital during the past ten years occurred among the 100 patients with infectious asthma. Death was chiefly due to asphyxia caused by suppuration in the bronchopulmonary system. Whereas the deleterious action of opiates in certain cases of asthma has been generally attributed to nonspecific action on bronchial secretion, respiratory center and on cough reflex, the question is still open for discussion whether aspirin acts specifically on an allergic basis or by an unspecific mechanism. It is known that aspirin-sensitive patients belong, as a rule, to the severe, intractable group of intrinsic asthmatic patients who lack other clinical hypersensitivity (Van Leeuwen,[59] Rackemann[42]), as it was also found in this investigation.

It appears that generally accepted diagnostic criteria for death from asthma are as questionable as they are for asthma during life. Since excessive bronchorrhea may be responsible for the asphyctic deaths of pa-

tients with chronic bronchitis, silicosis, penumonia and lung abscess, death in an "asthmatic attack" (Thieme, Sheldon[53]) does not indicate the nature of the asthma. Moreover, patients who die from asthma usually belong to the intrinsic type. Their life history has been in many cases characteristic of infectious asthma rather than of allergic asthma.[12,20,23,32,42,53]

In these patients, the pulmonary lesions are usually of that type which is commonly found in chronic nontuberculous infections of the lungs. Nevertheless, pulmonary suppuration, bronchiectasis and fibrosis, emphysema and atelectasis have been considered as pathological features of asthma if the patient presented asthmatic symptoms during life. The same can be said with regard to certain histological findings such as eosinophilic infiltration and hypertrophy of bronchial structures. Although they too may occur in a variety of conditions, especially of infectious nature, without asthmatic manifestations,[27,53] they are still considered as indicative of bronchial asthma. Actually, they are of little value in the pathological differential diagnosis between infectious and allergic asthma. Other histologic findings, such as sacculation of bronchi,[13,53] appear to be more significant because they strongly suggest an infectious process, even if reported in deaths from bronchial asthma without complications.[58] The presence of sticky material, plugging bronchi and bronchioles, has been considered as another characteristic feature of fatal asthma.[42] It needs hardly be mentioned that mucopurulent bronchial secretion, due to pyogenous infection, may also lead to plug formation and to death from asphyxia, with or without asthmatic symptoms.

It appears that the interpretation of all these pathologic changes as being complications of bronchial asthma is not warranted. In patients with infectious asthma, in which allergy seems to play no major part, the assumption that bronchiectasis and other lesions are due primarily to allergy confuses the true situation. It is appreciated that in certain instances allergy and other mechanisms besides infection may be responsible for pulmonary lesions.[1,41] This does not change the stand which has been taken here, and is supported by previous observations,[20,23] that bacterial infection as such is the direct cause of many cases which have been and still are considered as bronchial asthma, allergic bronchitis, and allergic bronchiectasis.

The conclusions to be drawn from this study in practical respect are obvious. Accepting an acute bronchopulmonary infection as the origin of infectious asthma, a rational therapy of this disease has to consider, most of all, its initial stage. The early elimination of the "focus of infection" in the lower respiratory system, by all therapeutic measures at our command, is the safest way to prevent its perpetuation, regardless of immunologic mechanisms possibly involved.

If, in the future, intelligent and conscientious consideration will be given to this problem, the high incidence of "chronic bronchitis" and of "infec-

tious asthma" will be avoided, and a great deal will be accomplished in the prevention of bronchiectasis.

SUMMARY AND CONCLUSIONS

1. One hundred selected cases of infectious asthma have been studied as a group. The incidence, age, cause and clinical-pathological features of this condition have been correlated.

2. The analysis of this series and the findings of other comparable studies indicate that infectious asthma, under its various terms, is basically chronic bronchitis, the pathogenic factor being nonspecific, chronic, bronchopulmonary infection. The asthma in this condition is a symptom, and should be considered apart from allergic bronchial asthma. Allergic manifestations, which are present in certain cases of infectious asthma, are coincidental in character.

3. Rational therapy of infectious asthma must be directed toward the earliest possible elimination of the pulmonary infection itself from which the disease originates. All modern therapeutic measures should hereby be used, especially the sulfonamides and antibiotics. By these means, serious pulmonary diseases, such as bronchiectasis, may be prevented.

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(Continued on Page 377)

Department of Clinical Pathology and Laboratory Procedures

THE ETIOLOGY OF CHRONIC URTICARIA

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El Paso, Texas

DURING the last fifteen years, as knowledge concerning the management of allergic diseases has become more widely disseminated among the general practitioners, the specialist in allergy has come to see fewer and fewer cases of simple, short-duration urticaria. Many of the obvious food cases are successfully managed by simple trial diets and, indeed, many patients have learned to solve their own problems without recourse to medical advice. The widespread use of the anti-histaminic drugs has likewise contributed its share to the control of the simple cases of urticaria. For some time now, the patients with urticaria whom we have seen are highly selected. The selected group includes those in whom simple trial diets and perhaps skin testing have been of no avail, those in whom symptoms have persisted for a number of months and sometimes years, and those in whom the anti-histaminic drugs have been without benefit.

In my opinion, based upon my experience with this group of cases, the most common etiologic factor is infection. Almost all of these patients will present some other definite evidence of a low-grade, chronic inflammatory reaction. This is especially true if blood count, sedimentation rate and Weltman coagulation tests are made. In almost every case one will find some evidence of an inflammatory response in the blood, either an elevated blood count, sedimentation rate or a Weltman shift indicating inflammation. Sometimes all three of these are abnormal. It then becomes a matter of searching out the location of the chronic infection by the usual and appropriate means. In other instances, routine examinations of the stools will reveal parasitosis. Occasionally, one encounters a patient with a definite decrease in prothrombin level in the blood, not associated with infection, on whom it is appropriate to try vitamin K therapy.

Without presenting a statistical analysis, I am sure that after adopting this viewpoint and approach in the chronic urticarias, that we relieve a good many more patients than were relieved in the past by the more conventional allergy approach. Within the past two years, two patients have been relieved of their chronic urticaria by treatment of gall-bladder infection. One has been relieved by the eradication of a dental infection. One has been relieved by appropriate therapy to a chronic prostatitis. Several have been relieved by penicillin or sulfadiazine therapy, or a combination

of the two, when no specific infection could be found yet when there was a definite indication of such infection on examination of the blood. Two have been relieved by clearing chronic urinary tract infection. One has been relieved by the eradication of giardia from the intestinal tract and gall bladder. Two with very low serum proteins, apparently the result of a too rigidly limited diet following previous skin testing of foods, were relieved by the simple expedient of placing them on a completely unlimited diet, with the assurance that they did not have a lifetime intractable allergic problem.

I make these few remarks to emphasize the plea for more careful diagnostic consideration of the chronic urticarial problem. It is my conviction that a careful diagnostic program is a great time saver. We are all too prone to be guided by a statistical consideration of large numbers of cases. One will readily admit that such cases are indeed a small percentage of the sum total of all urticarias, and we are therefore likely to leave such problems for consideration until everything else has failed. However, in the light of the individual patient the situation is exactly reversed. The patient's case is 100 per cent of those cases in which he is interested. The correct answer for his particular problem is his sole objective. We should therefore consider all possibilities for each case and not limit ourselves to the most frequent or simplest etiological explanation.

We feel that a more general use of laboratory aids will materially improve one's ability to detect the possibility of such etiologic factors.

THE SIGNIFICANCE OF CHRONIC BRONCHITIS IN INFECTIOUS BRONCHIAL ASTHMA

(Continued from Page 375)

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FALL GRADUATE INSTRUCTIONAL COURSE

This course is presented to provide a more comprehensive understanding of the many manifestations of allergy so commonly encountered by both the general practitioner and specialist and to emphasize methods of diagnosis and treatment of allergic diseases so that the physician is prepared to give the greatest aid to his patient.

Monday, November 3, 1947

FUNDAMENTALS OF ALLERGY

8:30- 9:30	F gistration.
9:30- 9:45	Address of Welcome, Dean Stanley Dorst.
9:45-10:30	"The Physiology of Allergy," Dr. Fred W. Wittich.
10:30-11:15	"Immunological Aspects of Allergy," Dr. Mary Loveless.
11:15-12:15	"The Clinical Significance of Recent Chemical Studies of Allergens," Dr. Harry S. Bernton.
12:15- 1:15	"Basic Principles of Allergy"—Moving Pictures, Dr. Bret Ratner.
2:15- 3:15	"Psychosomatic Factors in Allergy," Dr. John H. Mitchell.
3:15- 3:45	"Present Status of Antihistamine Drugs," Dr. Jonathan Forman.
3:45- 5:00	"Pharmacology of the More Important Drugs Used in Allergy," Dr. D. E. Jackson.
7:00	Informal Dinner—Speaker: Dr. Hal M. Davison.

Tuesday, November 4, 1947

FUNDAMENTALS OF ALLERGY

9:00- 9:30	"X-Ray in Allergy; Diagnosis and Treatment," Dr. Paul Moore.
9:30-10:30	"Bacterial Allergy," Dr. E. E. Ecker.
10:30-11:15	"Food Allergy," Dr. Hal M. Davison.
11:15-11:45	"Balanced Diet," Dr. William B. Bean.
11:45-12:30	"Elimination Diet,"Dr. Herbert J. Rinkel.
12:30- 1:15	"Physical Allergy," Dr. Harold A. Abramson.
2:15- 3:15	"The Preparation and Standardization of Extracts," Dr. Morris A. Kaplan.
3:15- 4:00	"Skin Testing: Technique and Interpretation," Dr. William F. Mitchell.
4:00- 4:30	"History Taking," Dr. J. Warrick Thomas.
4:30- 5:00	Demonstration, Dr. Charlotte Wiedemer.

Wednesday, November 5, 1947

RESPIRATORY ALLERGY

9:00- 9:45	"Pathology of Asthma," Dr. Milton G. Bohrod.
9:45-11:15	"Bronchial Asthma: Diagnosis, Management and Treatment," Dr. Leon Unger.
11:15-12:00	"Aerosol Treatment of Asthma," Dr. Harold A. Abramson.
12:00-12:30	"Bronchoscopy in the Treatment of Asthma," Dr. Howard L. Stitt.
12:30- 1:15	"Cardiac Asthma and Cor Pulmonale," Dr. J. Harold Kotte.
2:15- 3:15	"Allergic Bronchitis, Bronchiectasis and Loeffler's Syndrome," Dr. Vincent J. Derbes.
3:15- 3:45	"Allergic Rhinitis," Dr. French K. Hansel.
3:45- 4:15	"Aural Allergy," Dr. Hugh A. Kuhn.
4:15- 5:00	—"Ocular Allergy," Dr. A. D. Ruedemann.
8:00-10:00	Clinic.

FALL GRADUATE INSTRUCTIONAL COURSE

Thursday, November 6, 1947

HAY FEVER

9:00- 9:30 "Botany of Hay Fever Plants," Dr. Roger P. Wodehouse.

9:30-11:00 "Hay Fever: Diagnosis, Treatment and Management," Dr. George E. Rockwell.

11:00-11:45 "Pollen Respiratory Allergy with Negative Cutaneous Reactions," Dr. M. Murray Peshkin.

11:45-12:45 "Mold Allergy: Symptoms, Diagnosis and Treatment," Dr. Homer E. Prince.

12:45- 1:15 "Pollen Counts and Demonstration," Dr. Charlotte Wiedemer.

2:15- 3:15 "Vascular Allergy," Dr. Milton G. Bohrod.

3:15- 5:00 "Clinical Use of Histamine," Dr. Bayard T. Horton.

Friday, November 7, 1947

DERMATOLOGIC ALLERGY

9:00- 9:45 "Atopic Dermatitis," Dr. Stephan Epstein.

9:45-10:45 "Contact Dermatitis," Dr. Leon Goldman.

10:45-11:25 "Urticaria," Dr. R. F. Hughes.

11:25-12:20 "Soap and Other Detergents," Dr. Irvin H. Blank.

12:20- 1:30 "Drug Allergies," Dr. Ethan Allan Brown.

2:30- 3:00 "Joint Allergy," Dr. Bela Schick.

3:00- 4:15 "Neuro Allergy including Migraine," Dr. Foster Kennedy.

4:15- 5:00 "Unusual and Obscure Conditions of Allergies," Dr. C. R. K. Johnston.

Saturday, November 8, 1947

PEDIATRIC ALLERGY

9:00- 9:45 "Management of the Pre-Allergic Child," Dr. Bret Ratner.

9:45-10:30 "Characteristics of the Allergic Child," Dr. A. B. Schwartz.

10:30-11:45 "Special Problems in Treatment and Management of Asthma in Children," Dr. George Piness.

11:45-12:45 "Infantile Eczema," Dr. Albert V. Stoesser.

12:45- 1:30 "Gastro-intestinal Allergy in Children," Dr. Orval R. Withers.

On Tuesday, Thursday and Friday evenings from 8:00-10:00 p.m., there will be instructors in Parlors A and B, Netherland Plaza Hotel, so that students may visit, ask questions and have informal discussions.

Speaker at Large and Director of Round Table Discussion, Dr. George L. Waldbott.

Make all reservations for the Course and hotel accommodations directly with the secretary, Dr. Fred W. Wittich, 423 La Salle Medical Building, Minneapolis, Minnesota. When requesting your reservation, please state the exact time of your arrival and departure and whether you want a single room or wish to share one with another registrant. The number of single rooms is limited. The fee for the Course is $100.

Editorial

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HORSE IMMUNOLOGY FOR ALLERGISTS

Allergists and immunologists share to a large extent the problems of theoretical conception and of experimental approach. A series of papers from Heidelberger's[1] laboratory concerning the immune response of the horse, just published, merits a word of comment here, because it sheds light on three aspects of immune reactions, of which—we suspect—our readers are not always aware: namely, the multiplicity of antibodies, the occurrence of non-precipitating antibodies, and the influence of the site or mode of introducing antigens upon the immune response.

Two kinds of precipitating (and protecting) antibodies are known to be formed by the horse. One is typically represented by the antitoxins. They are water soluble and give the characteristic prozone effect of the toxin-antitoxin flocculation. The other is typified by the antibodies versus the carbohydrate antigens of bacteria as, for instance, of pneumococci. They are water-insoluble and do not give prozone effects.

In one of Heidelberger's horses, that on a previous intravenous immunization with rabbit globulin produced precipitating antibody, a series of intradermal and subcutaneous injections with the same antigen evoked a non-precipitating antibody. Similar observations have been recorded before—first by Coca and Kelly[2] in rabbit sera versus H. influenzae. Antibodies can be traced *in vitro* either by the inhibition of the reaction of "normal" antibody or by the demonstration of the addition of nitrogenous matter to corpuscular antigen after contact with the serum. Recently, non-precipitating antibodies have also been found in man: namely, in anti-Rh sera[3] and in sera versus Shiga and typhoid bacilli.[4] It is perhaps permissible to hope that the study of these antibodies will help in the understanding of the differences between "allergic" and "immune" mechanisms.

It is an old experience that antitoxin production in horses depends greatly on the route of immunization; on subcutaneous injections abundant antitoxin is formed; intravenous injection is not successful. Heidelberger noted similar differences in the response to his proteinic antigens: anti- (rabbit-) albumin antibodies of the antitoxin type were freely produced only upon subcutaneous and not after intravenous introduction of the antigen. However, the precipitin type of antibody versus rabbit

(Continued on Page 396)

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Progress in Allergy

RESPIRATION
A Review of Recent Literature

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The textbooks concerned with the subjects of bronchial asthma take for granted, in their readers, a knowledge of the mechanism of normal and abnormal respiration. Since the advances in this field have been many during the last decade, a partial review of the subject would seem to be necessary, especially since the facts now known will not be part of medical literature for some years. The present paper is concerned with some of the more important discoveries, and especially those of which knowledge is necessary for the full understanding of conditions treated by the internist specializing in allergy.

For the anatomy of the lung, the classical monograph by Miller[43] is required reading. For the physiology, it would be difficult to improve upon Wright.[58] For general analysis, reference must be made to Gray[29] or to Richards.[51-53] Since all of the work of recent years on respiration cannot possibly be reviewed, a bibliography listing the more important papers by Alexander and Kountz,[1] Anthony,[2,3] Barach,[4,5] Christie,[10-13] Cournand,[14-18] Hermannsen,[33] Hurtado,[34,35] Knipping,[37] and Kountz,[38,39] will be found at the end of this paper.

Respiration, undoubtedly one of the most complex of the body functions,[27] is controlled by a number of factors, the immediate being the bilateral intracranial centers in the medulla and the bilateral extracranial carotid sinus mechanisms at the bifurcation of the carotid arteries. The distant controls include the higher centers and their hidden and overt effects as well as the tissue enzymes. The intermediate controls are placed in the cardiac and the vasomotor centers, the aortic arch, the lung itself, as well as the chest wall. The multiple factors involved form an intricate complex of physical, chemical, and neuromuscular stimuli associated with systems as diverse as the excess or lack of either carbon dioxide or oxygen, the rise or fall of the blood pressure, the metabolic rate, the composition and reaction of the blood, and the presence or absence of the respiratory enzymes. If to this incomplete list we add the effects of anatomical or pathological abnormalities, acute or chronic infections, neoplasm, congestion or collapse, and allergic sensitivity, all of which reflectly may stimulate or depress respiration, the problem becomes complex indeed.

To begin with the individual cell, respiration is a cycle in which molecular oxygen reacts with bivalent iron, which, oxidized in turn, reacts with the tissues and is again reduced to bivalent iron. This process occurs on the surface of the cell and as such may be inhibited by substances such as narcotics, which, themselves incapable of being used in this manner, crowd the material to be oxidized away from the surface. The process, too sluggish for practical purposes, must be mediated by enzyme activity; that is, by respiratory ferments. Of these, if we limit ourselves to internal respiration, we have Keilin's Cytochrome C and Warburg's yellow enzyme,[56,57] now known to represent five enzymes; flavoproteins of which the pigment portion consists of the phosphoric acid ester of riboflavin.[7] Not only does the acceptance of oxygen require enzymatic activity, but the release of carbon dioxide is also accelerated by an intracellular enzyme, carbonic anhydrase affecting carbhaemoglobin.[54] This knowledge may appear purely theoretical and relatively un-

important, except for recent work which demonstrates the changes which may occur following the injection of Cytochrome C into the body.

Proger and his colleagues,[48-50] as a result of being able to demonstrate that the Cytochrome C content of the heart, brain, liver, and kidney might be far below that required for the maximal activity of the Cytochrome oxidase present, injected the material intravenously and demonstrated that it was stored in these organs and produced a significant increase in the tissue uptake of oxygen. Under conditions of severe anoxia (3 per cent oxygen and 97 per cent nitrogen) there was a striking increase in survival time in rats, previously injected with Cytochrome C, as compared with control animals. It was then demonstrated that the extreme subjective disturbances, which occasionally occur with anoxia, induced by a mixture of oxygen (10 per cent) and nitrogen (90 per cent) could be prevented by the injection of 25 to 30 mg. of Cytochrome C. Electrocardiogram changes were also demonstrable. In intermittent claudication, seven of thirteen patients showed striking improvement; three, moderate effects; and three, no effect, the increased exercise tolerance continuing for almost one year after the last injection. During an initial control period following the injection of an inert solution for eight days, there were no effects.

Our own experience[8] with patients suffering from dyspnea associated with extreme emphysema corroborates the salubrious effects of Cytochrome C injection.

The intermediate mechanisms can be discussed in turn, and then correlated since none acts independently of the others. The excess of carbon dioxide is affected by, and will affect, the reaction of the blood, the aortic body of the aortic arch, the carotid body, and also the respiratory center, and will increase first the depth and then the frequency of respiration. Since the H-ion concentration of the blood is diminished during gastric secretion, bicarbonate ingestion, or an alkaline-ash diet, all three factors will depress respiration until the tendency toward alkalaemia has been compensated.

Conversely, during intestinal digestion, ammonium chloride ingestion and acid-ash diets, as well as in diabetes and starvation, respiration is stimulated until the tendency toward acidemia has been checked. It should be noted that both of these descriptions are over-simplified and neither is completely true. As stated by Gray,[20] if test subjects are made to breathe varying percentages of carbon dioxide under conditions of rest, exercise, anoxia, and ammonium chloride acidosis, the result curves are linear and with similar slopes but differing positions. Since the constancy of the slope of the curve indicates that a given increment of stimulation produces the same increment in response, independently of the conditions, this must be taken as evidence of unaltered irritability suggesting the influence of an additional factor.

The effects of oxygen lack depend upon whether they are gradual or sudden in onset. When they are slow, as seen in changes of altitude, no symptoms occur until a height of approximately 12,000 feet is reached, at which point the increase occurs in rate and not in depth of respiration, the increased pulmonary ventilation washing out the carbon dioxide, and depressing respiration. The successive stages of this cycle take place as follows: The oxygen lack stimulates respiration, which increases pulmonary ventilation, resulting in lowered alveolar carbon dioxide, which in turn lowers arterial oxygen and causes alkalaemia, depresses respiration until the carbon dioxide tension increases, or the oxygen lack is again felt. Unfortunately, oxygen lack greatly depresses the isolated respiratory center, and if the vagi and sinus nerves are severed, the same mixture rapidly causes respiratory paralysis. In the intact subject, therefore, oxygen lack acts chiefly upon the chemo-receptors of the aortic arch and carotid sinuses[20] and so reflexly stimulates increased respiration. The respiratory center appears to be much more sensitive to carbon dioxide excess alone than to carbon dioxide excess combined with oxygen lack.

The actions of oxygen excess must be mentioned since they are not as generally

appreciated as are the effects of carbon dioxide excess. Mixtures containing oxygen (60 per cent) can be breathed indefinitely and cause no change in pulmonary ventilation, metabolic rate, blood pressure, or mental activity. Animals exposed to mixtures containing oxygen (75 per cent) develop pulmonary congestion and consolidation and die within a few days. Animals exposed to pure oxygen at several atmospheres pressure, develop coma and die rapidly. Men exposed to pure oxygen at four atmospheres develop a fall in blood pressure, convulsions, and faintness within an hour. The poisonous effects are due in part to the retention of oxygen. The oxygen dissolved in plasma normally totals 0.3 per cent. In pure oxygen, at a pressure of one atmosphere, this dissolved oxygen increases to 2 per cent, sufficient to meet the resulting oxygen requirements in the tissues which are about 3 c.c. per 100 c.c. of blood flow. Since the oxyhaemoglobin is not reduced, no carbhaemoglobin can be formed and the carbon dioxide is therefore retained in the tissues in toxic amounts.

The respiration of pure oxygen can be used to measure the effectiveness of aeration of the pulmonary system. The index known as the pulmonary emptying rate is attained by having the subjects breathe pure oxygen for seven minutes. The percentage of nitrogen which remains in the alveolar air is a significant factor, and in normal subjects is less than 2.5 per cent while in emphysematous conditions, the index may be over five per cent. The relation between the minute pulmonary ventilation and the amount of oxygen absorbed, expressed as the difference in per cent concentration of oxygen between inspired and expired air, is termed the oxygen utilization co-efficient. Anthony[2,3] has taken the reciprocal of pulmonary ventilation/oxygen consumption as the ventilatory co-efficient. In normal individuals, the co-efficient of oxygen utilization varies from 4.5 to 5.5 per cent, with an increase of 0.5 per cent for mild or moderate exercise. In bronchial asthma, the patient breathes a much larger volume of air for a given oxygen absorption and the oxygen utilization decreases occasionally as low as 3.0 to 3.5 per cent.

At this point, the effect of hyperventilation, often seen in emotional patients subject to bronchial asthma, should be reviewed.

Apropos of the antiquity of the descriptions of the hyperventilation syndrome is a passage taken from DuLaurens in 1559[4] who says, "Melancholoke folke are commonly given to sigh because the minde being possessed of great varietie and store of foolish apparitions, doth not remember or suffer the partie to be at leisure to breathe according to the necessitie of nature, whereupon she is constrained at once to sup up as much aire as otherwise would serve for two or three time; and this great draught of breath is called by name sighing, which, as it were, a reduplicating of the ordinary manner of breathing. In this order it falleth out with lovers, and all those who are very busily occupied in some deep contemplation. Sillie fooles likewise, fall into wonder at the sight of any beautiful and goodly picture are constrained to give a great sigh, their will (which is the efficient cause of breathing) being altogether distracted and wholly possessed with the sight of the image."

Two or three minutes of voluntary hyperpnoea will be followed by a period of apnoea, and then by a phase of periodic breathing. If continued for longer than a few minutes, the over-ventilation causes a leukocytosis, hyperglycemia and a diuresis, with acetone bodies. The lowered carbon dioxide tension acts directly upon the arterioles of the skin, which becomes white and cold. There is undoubtedly a relationship to epinephrine absorption and effect if the medication is injected for a concomitant wheezing. If the subject takes pure oxygen and carbon dioxide (5 per cent) during a period of hyperventilation, no ill effects occur. If pure oxygen is taken alone, apnoea, which may last up to eight minutes, appears, and respiration then recommences of itself.

That the act of forced hyperventilation should cause many primary and secondary effects upon the cardiovascular and nervous systems should not surprise us. As

Mills[44] said, "The primary phenomenon may be considered as a powerful, neuronic discharge, whose precise distribution is entirely unknown, but which greatly increases the respiratory movements. The consequent over-ventilation of the lungs, the altered chemical composition of the blood; and the muscular movements involved in breathing produce large rhythmic fluctuations in intra-thoracic and intra-abdominal pressures, which, we can agree, affect the circulation of the blood. The chemical changes may directly affect the activity of different levels of the central nervous system, and also by direct or reflex action on the heart and vascular calibres, produce alterations in the circulation; and such alterations in the circulation, produced directly or indirectly, may alter blood flow through parts of the central nervous system and hence produce chemical changes there." In discussing the phenomenon that the hypernoea may continue, he goes on to say that, "An increased venous return induced particularly by diaphragmatic over-ventilation may be the cause of such continued dyspnea, the hypernoea being decreased or absent if the venous return is limited by the occlusion of blood in the lower limbs. Some subjects are persistently hypernoeic after forced breathing, whatever measures are taken to exclude, diminish, or increase the possible modes of stimulation of the respiratory center. The latter type of hypernoea is independent of acapnia and the giving of an alveolar sample, and quite uncorrelated with blood pressure changes; it is undiminished when the venous return is restricted by occlusion of the blood in the lower limbs; it is uncorrelated with modifications of electrical activity of the cerebral cortex induced by forced breathing. It is therefore suggested in part by exclusion and in part through some positive lines of evidence that it results directly from that same cortical activity which is initially responsible for the forced breathing."

The nervous pathways involved are three, all of which merit brief review.

The action currents of the single fibres of the phrenic and intercostal nerves and of single motor units of the muscles involved demonstrate that during respiration at rest, the muscles are being stimulated subtetanically, the impulses reaching them at a rate of 25 per second. The discharge is asynchronous, the motor units out of phase, and since only a proportion of the fibres are stimulated, the muscle pull is steady. For deep respiration, the impulse discharge rate reaches as high as 100 each second, affecting large numbers of motor units at a more synchronous rate, causing full tetanus and more forceful contraction of the diaphragm and the external intercostal muscles. Direct recording of the electrical changes in the intercostal muscles demonstrates active contraction of the expiratory muscles during the expiratory phase of deep respiration.[22]

A second set of impulses, inhibitory in nature, proceed, during inflation from the pulmonary tissues along the varus to the respiratory center, eventually causing inhibition of inspiration, while during expiration, a corresponding set of fibres send increasing stimulating impulses, eventually causing the cessation of expiration and the initiation of inspiration. This effect, the Hering-Breuer reflex,[32] will not occur if both vagi are severed, respiration then remaining a series of slow, deep inspirations and expirations.

A third set of impulses arises in the smooth muscle fibres of the bronchi, which receive fibres from the sympathetic system, affecting dilatation, and from the vagi, affecting constriction. The afferent impulses in the vagus reflex controlling asthma may arise not only from the nose (Brodie-Dixon reflex), the irritation of non-specific irritations, but also from non-passive expiration as in chronic cough, and from the local effects following allergen inhalation or histamine release, due to local infection as well as to blood stream changes following the ingestion or injection of allergens.

The nerve pathways for the Brodie-Dixon reflex described above have been studied and there is much experimental and factual evidence to support the view

that an abnormal nasal condition can, when the "soil" is suitable, give rise to reflex bronchial asthma. Myers[45] has shown by micro-dissection that the pathways for the reflex probably pass through the anterior ethmoidal nerve, the first division of the fifth (trigeminal) nerve, the gasserian ganglion, and the nucleus of the fifth nerve in the upper part of the pons. From here, the fibres can be traced to the nucleus ambiguus in the medulla. Here the vagus and glossopharyngeal nerves originate. Other fibres from the nose pass through the sphenopalatine ganglion to reach the nucleus of the vagus. In patients in whom this reflex is thought to operate, the spraying of the nasal mucosa with a cocaine solution (2 per cent) should afford almost immediate, although transient, relief from the wheezing.

Our own work corroborates such effects occasionally strikingly dramatic in patients with status asthmaticus. Sensitivity to cocaine must of course be excluded. As a clinical example in this regard, Shields[55] describes a patient with left-side trigeminal neuralgia and bronchial asthma, who, following the division of the sensory route of the gasserion ganglion abolished the attacks of bronchial spasm in the left lung, while typical signs of bronchial asthma persisted on the right side.

Since the airation of the blood in the lesser circulation depends on its quantity in the pulmonary bed, it should not surprise us to discover that an additional mechanism mediated by another set of reflexes operates in this area. This pulmonary hemodynamic mechanism has been described by Parin,[46] who, by a most ingenious set of experiments, revealed that a rise in pressure within the vessels of the isolated lung was always accompanied by a fall in pressure in the systemic arterial bed, and in most cases, by a slowing of the heart rate. It required only a slight rise in pulmonary pressure to produce a very measurable decline in arterial pressure, the two being proportional and associated with a slowing of the heart beat. The receptors of these reflexes, probably located in the arteries or veins of the lesser circulation, act in two ways: first, to protect the weaker muscles of the right heart from overwork by lowering the cardiac capacity and producing vasodilatation with a fall in systemic blood pressure; and, second, to increase the capacity of blood reservoirs whenever the pulmonary circulation is taxed. Its second function acts undoubtedly to prevent pulmonary edema.

That the pulmonary arteries and veins not only protect the heart but also act as an "accessory heart" can be concluded from the work of Mac Klin,[41] who shows that the vessels are surrounded by expanding and contracting air spaces, which causes a rhythmic increase and decrease in their calibre with each respiratory cycle. In inspiration, the vessels become elongated and widened by the traction of the fibres connecting their walls with the enveloping air spaces. In expiration, they are shortened and narrowed by the recoil of their specialized elastic fibres. In inspiration, therefore, their blood content is increased and in expiration, decreased. The heart responds to the advantage of enlarged vascular capacity by beating faster and increasing its output into the pulmonary vascular bed, which is therefore a bridge for the blood, which must flow in sufficient amounts if systemic vessels are to be supplied properly. This ability on the part of the lesser circulation to adapt itself to the demands of long and continuous physical exercise is directly due to the distensibility and contractibility of these vessels as due to the expansion and contraction of the air sacs and the function of "accessory heart" taken on by the vascular bed.

An interesting correlation not generally known because sympathectomy is performed uncommonly for the treatment of bronchial asthma in this country, is suggested by the work of Hagen.[31] In seven patients, for whom the cervical ganglion had been removed surgically for the treatment of bronchial asthma, the sections of these ganglions showed the majority of the ganglion cells to present pathological changes.

Vacuolation and granular degeneration are seen in the body of the ganglion and

spherical terminal formations in the processes point to the presence of pathological irritation. There is accumulation of pigment, as well as nuclear changes in the cells. The author feels that increased appearance of multinuclear ganglion cells and the pathological changes observable in them represent another degenerative process in bronchial asthma. He feels that the microscopic changes indicate not only that bronchial asthma is a "functional" disorder, but that serious organic changes co-exist in the sympathetic nervous system, and that these changes in the sympathetic cervical ganglion are the causes of the secondary symptoms of asthma. Such disturbances in the development of the sympathetic system may be decisive in the constitution of the asthmatic patient and may precede the asthma, be caused by it, and perhaps directly cause it in a reciprocal relationship.

The adaptations due to exercise are capable of simple review.[47] The pulmonary ventilation is increased by emotional tension, by the increase of carbon dioxide in the blood, by the rise in body temperature due to the additional metabolism, and reflexly from the engorged right side of the heart. Unless the blood pressure is raised or lowered rapidly, it has no immediate noticeable effect upon the mechanism of respiration. Other factors of less importance are those caused by pain, thermal stimuli, swallowing and also sleep, during which respiration is usually depressed and alveolar carbon dioxide usually considerably higher than during waking periods.

For the evaluation of the role of the psychological factors in respiration, there are a number of reviews which vary from the purely psychoanalytical to the most objective type of laboratory test. The effects of emotion upon the movements of the diaphragm have been described as seen fluoroscopically by Faulkner.[23,25] While responding to questions evoking unpleasant states, the diaphragmatic excursions were constantly limited to one-half inch; while responding to pleasant mental pictures, the range of respiratory diaphragmatic movement extended to three and one-half inches, during a time that the patient was not conscious that he was being examined fluoroscopically for this purpose. These same patients had an associated cardiospasm. Faulkner has also demonstrated the influence of suggestion on the size of the bronchial lumen. During bronchoscopy, conversation about indifferent subjects caused no changes in the lumen of the bronchioles, while thoughts of insecurity and frustration caused spasm and a narrowed lumen, while suggestions of pleasurable nature caused bronchial relaxation. In a second patient, the spasm was associated with dyspnea, choking and wheezing. The psycho-biological aspects of respiration have been discussed by Binger,[6] who stresses the dyspnea associated with anxiety states, and also by Christie,[10-13] who contrasts the patients with anxiety neuroses, who present an irregular shallow type of respiration with the patients who present conversation hysterias and have a tendency toward hyperventilation. The relationships between anxiety states and hyperventilation have been discussed in detail by Kerr,[36] in one of whose patients 90 seconds of hyperventilation would cause an asthmatic attack.

The mechanism of cough is so closely related to that of respiration and to the chief presenting symptoms of so many of our asthma patients, that it, too, should be discussed.

Fenichel[26] in his analysis of the psycho-pathology of coughing lists six types of reactions. He points out that the severe organic cough of chronic states leads to an introversion. An intolerant patient with a chronic cough tends to become irritable, restless, angry, and accusatory of others. In the second type of patient, the cough becomes a substitution vent for relieving an inner pressure caused by repressions. In the third type of patient, whose respiratory tract has acquired a particular sensitivity to psychic stimuli, a cough may be imitated or a repetition due to an earlier experience in which coughing occurred. A fourth type is a psychogenic cough related to the "tics" as seen in a nervous person who does not wish to speak, and occasionally in audiences who do not wish to hear. The fifth type is

the cough, organic in origin but psychogenic in its persistence; and lastly, a type in which combined effects may be noted.

The internist, who sees patients with chronic bronchial asthma and emphysema, must have a clear picture of the respiratory readjustments which occur in his condition. The loss of elasticity of the lung tissues leads to a distension and a marked increase in the volume of the functional residual air. In normal individuals, this ranges from 35 to 40 per cent, but in emphysema may be as great as 70 to 80 per cent. The vital capacity is therefore reduced, and although at rest it may be quite similar to the normal, on exertion, the volume cannot be properly increased and respiration is shallow and rapid. In the more severe type of case, the resting tidal air and the vital capacity may approximate equality.

Meakins,[42] in his discussion on emphysema, shows how, with the loss of pulmonary elasticity, the natural elastic recoil of the lungs is absent, and the lung tissue must be compressed by an active expiratory effort with the generation of a positive intrapleural pressure, to which the thoracic cage in man is wholly unsuited. The diaphragm is a muscle of inspiration, and has not been constructed to resist an increase in intra-thoracic pressure which is bound to displace it downward with an impairment of its tone and contractile range. The displacement of the diaphragm can be prevented only by contraction of the muscles of the abdominal wall. The abdomen is often relaxed and pendulous in these patients and cannot therefore be used as an accessory aid to respiration. The over-voluminous contents of the thorax do not permit the diaphragm to rise to its normal position at the end of expiration. The alveoli, therefore, are not equally ventilated, since the superficial alveoli are distended, ischemic and relatively functionless, but over-ventilated at the expense of the deeper, healthier alveoli, which are under-ventilated.

Slowly, but inevitably, circulatory readjustments take place. The small but definite pressure gradient between the vena cava and the right auricle is governed by the negative intra-thoracic or intra-pleural pressure. As this becomes positive, an increase in the venous pressure takes place, which, in turn, progresses to congestive failure. Inspiration is altered because the muscles are in the inspiratory position. The air inspired is wasted on the peripheral functionless alveoli. The lungs cannot relax passively, except as a result of unnatural, expiratory effort. The imperfect airation of the blood makes increasing demands for hyperventilation coupled with decreasing ability to ventilate.

Goggio[28] emphasizes the fact that there are two types of emphysema; the first, the postural or senile type, which occurs more frequently but is seldom of clinical significance; and the second, chronic, hypertrophic, or obstructive type, which has a younger age incidence, and in which the chief etiological factor is respiratory obstruction. Christie[10-13] states that in his experience, more than 90 per cent of the patients with the chronic hypertrophic type of emphysema give a significant history of asthma and chronic bronchitis. In one of the cases described by Goggio,[28] a patient with emphysema and an apparently normal vital capacity required twenty seconds to exhale the same amount of air as was exhaled by a normal subject in one and one-half seconds with ease, during which time the normal subject could expire 4 liters of air, while the patient could only expire 900 c.c. Goggio stresses the fact that, although the patient, on physical examination, may give no indication of any infective process in the lungs or of any asthmatic state, yet a careful history may reveal a formidable pulmonary infective prologue and may disclose indications of a possible bronchospastic factor. Among these, may be the paroxysmal nature of the dyspnea, its precipitation by emotion, the occasional presence of expiratory squeaks and groans, and the relief of the dyspnea for several months after an attack of pneumococcal pneumonia. The actual presence of the bronchospastic factor can be easily demonstrated when, immediately after physical examination has confirmed the absence of adventitious sounds in the chest, the administration

of a few minims of 1:100 epinephrine by nebulization results in a rise of vital capacity from 1,500 to 3,000 c.c. in 7 minutes. It is well to remember that marked bronchospasm can exist in the complete absence of adventitious sounds in the chest, and that the effect of epinephrine can be measured objectively for both diagnostic and therapeutic purposes.

Studies of oxygen saturation value in these emphysematous patients showed that it may be as low as 60 per cent, which corresponds to what might occur in an unacclimatized person at an altitude of 22,000 feet, a level at which mountain sickness occurs. The symptoms, therefore, of headache, dizziness, loss of appetite, weakness, fatigue, insomnia, tremor, tachycardia, and cyanosis, and occasionally episodes of disorientation, which occur in such patients, may be symptoms of mountain sickness and can be attributed to the attendant anoxia. The patients are relieved by oxygen therapy and the condition can be mitigated to some degree by an increase in the oxygen-carrying power of the blood. This mechanism may indeed explain our own success with the use of Cytochrome C in the emphysematous patients with dyspnea.

In some of the patients, who present a lowered vital capacity and dyspnea with no attendant pulmonary disease, the effect of pollen and other inhalants must be ruled out. In our own series, a group of patients with hay fever but with no clinical bronchial asthma presented this clinical syndrome.[9]

Advantage can be taken of some of these factors to distinguish between pulmonary and cardiac disease. Since forced expiration is a result of a muscular effort in which all the expiratory muscles normally participate, the vital capacity may be decreased through muscular insufficiency, although no abnormalities of circulation or of respiration exist. This muscular factor plays an important part in the diminution of the vital capacity caused by cardiac disease. It is important first to have a measurement of the patient's vital capacity taken standing, the highest readings being accepted. After a rest, the minimum duration of maximum expiration is measured by having the patient exhale as rapidly as possible following as deep an inspiration as he is capable of taking. The duration of the timed expiration is measured by stop-watch. After the vital capacity and the minimum duration of the quickest possible exhalation of the volume equal to the vital capacity has been measured simultaneously, the velocity of the spirometric respiration is obtained by dividing the vital capacity by the expiration time. The velocity of spirometric respiration is that air volume which enters the spirometer per second, representing the average of the quickest possible expiration.

It is indeed true that there is no relationship between the vital capacity (volume) and the expiratory pressure (strength), but the velocity of spirometric respiration depends on the vital capacity as well as on the expiratory pressure. Any decrease in vital capacity, due to cardiac disease, is characterized by prolongation of the expiration time, a decrease in the velocity of spirometric expiration, and, above all, by a decrease in the expiratory pressure, which in typical cases, is less than 50 per cent of the standard value. Decreases in vital capacity due to pulmonary disease are characterized by a greater prolongation of expiration time by distinct decrease in velocity of respiration and most of all by the fact that the expiratory pressure is normal or altered little if at all. The values obtained for normal individuals can be taken from the investigations by Gross,[30] who furnishes a table as a result of his studies.

Of interest to those who treat asthmatic patients are the comments of Eichler,[21] who found a tremendous, although transitory, increase in the histamine content of the blood plasma in cats breathing 10 per cent oxygen (equivalent to 18,000 feet), the circulation showing a rise from the normal of 0.056 to 0.12 to levels as high as 480 micrograms in the first 10 minutes, with a maintenance of such high levels for as long as one hour. Although the author does not suggest it, it may be possible that, due to lack of respiratory enzymes, or to oxygen absorption, similar lowered

oxygen tension may occur in asthmatic patients with severe emphysema and explain the effects of antihistaminic agents in some subjects and not in others.

It may be concluded from this brief review that respiration is a complex biological mechanism, stimulated, depressed and affected by many varied and diverse factors, no one of which operates alone. This multiple factor theory of the causation of respiratory ventilation is discussed in detail by Gray,[29] who states that while a number of factors exert independent effects upon respiratory ventilation, they are also mutually inter-dependent, so that a change in any one factor usually brings about changes in one or more of the other factors, the actual ventilation being defined as the algebraic sum of the partial effects of the separate agents. Since these lend themselves to mathematical description, it is possible to reduce them to working formulae. For those who wish to investigate these problems in the field of allergy, the four equations taken from this paper are listed below. The symbols used have the following significance:

pO_2—alveolar or arterial tension of O_2
pCO_2—alveolar or arterial tension of CO_2
FO_2—volumetric fraction of O_2 in dry, inspired air.
FCO_2—volumetric fraction of CO_2 in dry, inspired air.
H—H ion concentration of arterial plasma.
VR—alveolar ventilation ratio.
$VRpO_2VRpCO_2$, VRH—alveolar ventilation ratio as influenced by the definition of the subscript.
VRr—partial ventilation ratio due to the action of muscular reflexes.
MRR—metabolic rate ratio.
B—barometric pressure.
RQ—alveolar respiratory quotient.
O_2—oxygen content of the blood in volumes per cent.
O_2150—oxygen capacity of the blood in volumes per cent expressed as oxygen content of blood exposed to pO_2 of 150 mm. Hg.
BH $CO_37.41$—Bicarbonate content of volumes per cent of plasma from oxygenated blood at pH 7.41.

TABLE I. EQUATIONS AND MATHEMATICAL SYMBOLS

1. The general alveolar equation (relationship between pO_2 and pCO_2)

$$pO_2 = \frac{(B—47—pCO_2)\ (RQ.FO_2 + FCO_2) - PCO_2(1—FO_2(1—RQ)}{RQ + FCO_2(1—RQ)}$$

2. The general ventilation equation (relationships between actual ventilation and pCO_2):

$$\frac{47\ MRR(RQ + FCO_2(1—RQ)}{pCO_2 — (B—47)\ FCO_2}$$

3. The general respiratory pathway equation (relationships between H-ion and pCO_2):

$$PCO = \frac{H}{53.3} \qquad (16 + 2.3\ O_{2_{150}}) \quad (\log H — 1.59) + BHCO_{3_{7.41}} \quad +0.375\ (O_{2_{150}} — O_2)$$

4. The chemical ventilation equation (giving the sum of the partial effects of H-ion, pO_2, and pCO_2 on ventilation):

$$VR = 0.22H + 0.262\ pCO_2 + 18.0 + \frac{105}{10^{0.038}pO_2}$$

To use a paraphrase of Gray's own words in explaining the derivation of the formulae, "The first step consisted of the derivation on formal grounds of what has been called the alveolar equation, which defines all possible relationships between alveolar O_2 and CO_2 tensions for any barometric pressure, alveolar RQ, and for any inspired gas mixture.

The second step consisted of an analogous derivation on formal grounds of what has been termed the formal ventilation equation, which defines the possible relationships between the actual ventilation and the alveolar CO_2 tension for any condition of metabolic rate, alveolar RQ, and inspired gas mixtures.

The third step consisted of developing on empirical grounds what has been called the respiratory pathway equation, which defines the possible relationships between the arterial H-ion concentration and CO_2 tension, for any conditions of bicarbonate capacity, O_2 capacity, and arterial O_2 saturation.

The fourth step to be completed consists of the isolation and quantification of the partial effects on ventilation of the three important chemical agents, H-ion, pCO_2, and pO_2."

One of the major achievements of the present theory is that it resolves the most persistent and controversial question in the field of respiration: "Should H-ion or CO_2 be considered the true respiratory stimulus? From the standpoint of the multiple factor theory this question should be framed as follows: To what extent does each of the two agents influence ventilation? Equation 4, which accurately describes the extensive experimental data, provides a quantitative answer to this question. If it were true that only one of the two agents is the true stimulus, the procedure used to establish Equation 4 would have betrayed the fact by emerging with a co-efficient of zero for the inactive agent. Since neither of the co-efficients is zero, it must be concluded that both agents independently affect respiration."

The theory and the information given by this mathematical approach has proved itself useful, among other things, in estimating with accuracy the oxygen requirement at various altitudes, or equivalent altitudes, breathing varying percentages of oxygen, determining the efficiency of adding carbon dioxide to various gas mixtures, at differing altitudes. The information derived helps us understand, if only partially, the great many problems to be solved in pulmonary ventilation.

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(Continued on Page 396)

News Items

THE THIRD ANNUAL MEETING

The third annual meeting of the American College of Allergists was held June 6, 7 and 8 at the Hotel Senator, Atlantic City, just preceding the centennial session of the American Medical Association. The attendance exceeded that of all previous meetings. The attendance and enthusiasm aroused must be credited to Dr. Harold A. Abramson and his Program Committee, as well as to Dr. Charles Hyman, chairman of the Committee on Local Arrangements and his assistants. Although arrangements were made comparatively late, a very satisfactory number of manufacturers and distributors of products of interest to the allergists had advertisements in the printed program, as well as informal exhibits on the mezzanine floor during the session. Both of these new features helped to contribute to the success of the meeting.

The guest of honor, Dr. Gregory Shwartzman, Head of the Department of Bacteriology, Mt. Sinai Hospital, and Clinical Professor of Bacteriology, Columbia University, New York City, spoke at the Saturday afternoon session on "Phenomenon of Local Tissue Reactivity in Reference to Problems of Hypertensiveness and Evolution of Infectious Processes." The program was featured by the presentation of a round table and panel discussion on "Psychodynamics and the Allergic Patient" Sunday afternoon, June 8. Dr. Harold Abramson, Assistant Professor of Physiology, Columbia University, and Associate Professor of Allergy, Mt. Sinai Hospital, New York City, led the panel by reading a paper on the subject. The psychiatrists were represented on the panel discussion by the following: Dr. Frank Fremont-Smith, Medical Director, the Josiah Macy, Jr., Foundation, New York, New York, leader; Dr. Franz Alexander, Professor of Psychiatry, University of Illinois and Director, Chicago Institute for Psychoanalysis, Chicago, Illinois; Dr. O. Spurgeon English, Professor of Psychiatry, Temple University Medical School, Philadelphia, Pennsylvania; Dr. Sandor Rado, Clinical Professor of Psychiatry, College of Physicians and Surgeons, New York, New York; Dr. Edward Weiss, Professor of Internal Medicine, Temple University Medical School, Philadelphia, Pennsylvania; and Dr. J. A. P. Millet, Associate in Medicine, Columbia University, New York, New York. Representing the clinical allergists were: Dr. Rudolf L. Baer, Associate Attending Physician in Charge of Allergy Department, New York Skin and Cancer Unit, New York Postgraduate Hospital and Instructor in Dermatology and Syphilology, New York Postgraduate Medical School and Hospital, New York, New York; Dr. Ethan Allan Brown, M.R.C.S., London, L.R.C.P., England, Tufts College Medical School, Boston, Massachusetts; Dr. Hal M. Davison, Chief of Medical Division, Georgia Baptist Hospital, Atlanta, Georgia; Dr. Homer E. Prince, Associate Professor of Medicine, Baylor University School of Medicine, Houston, Texas; and Dr. M. Murray Peshkin, Instructor, College of Physicians and Surgeons, Post-Graduate Medical Extension, Columbia University, New York, New York.

As many members of the College as possible remained for the special session on allergy conducted by the AMA on Friday, June 13. There were about 450 present at this meeting. Dr. Harry L. Huber, Chicago, was chairman and Dr. Richard Kern, Philadelphia, secretary. The program was well balanced and highlighted by a panel discussion on "The Treatment of Asthma." Based upon the attendance and enthusiasm of this meeting one could reasonably expect that the Committee on Scientific Assembly of the AMA will seriously consider establishing a section on allergy and immunology in accordance with the request of the Academy and the American College of Allergists who appeared before the Reference Committee and the Committee on Section and Section Work. (J.A.M.A., July 20, 1946, Page 1000).

NEWS ITEMS

The American Society for the Certification of Allergists met at the Hotel Senator, Friday evening, June 6, at which time announcement was made of the names of those men certified in allergy who form the founders' group. Up to the present time 116 allergists have been certified.

At the business session of the Board of Regents, it was decided that the fourth annual convention in 1948 would be held at the Hotel Pennsylvania, New York City, March 12, 13 and 14. Dr. M. Murray Peshkin is chairman of the Committee on Local Arrangements for this meeting, and Dr. Harold Abramson, chairman of the Program Committee. Since the annual meeting is to be held more than two months earlier than usual, it is urged that all members make their reservations as soon as possible by writing to the Secretary. Due to the fact that this meeting will be held so early in the spring, it was decided that a Spring Instructional Course would not be held and that all efforts would be concentrated upon the Fall Instructional Course to be held under the auspices of the University of Cincinnati, November 3-8, inclusive. A special reduction of 25 per cent will be given to all members of the College for Instructional Courses.

The Advisory Committee, which met at the Hotel Gibson, Cincinnati, March 30, made a report to the members of the Board of Regents. A list of the speakers available through the Speakers Bureau, which was initiated by the College some time ago, will be sent to the secretaries of the various state societies designating the qualifications of members to lecture and speak on allergy.

At the business meeting of the Board two members were elevated to active fellowship. The College now has almost 700 members, and the standards for elevation to full fellowship have been raised.

Some of the newer antihistaminic substances were reported for the first time at this meeting.

During the past year the College has been unfortunate in the loss, through death, of the following: Dr. Harry Greditzer, St. Louis, Missouri; Dr. Andrew M. Smith, Egg Harbor City, New Jersey; and Dr. Erich Urbach, Philadelphia, Pennsylvania. Obituaries have appeared in the ANNALS and condolences have been sent to the families.

The by-laws, as read and approved by the Board of Regents and recommended for adoption by the members of the College at the San Francisco meeting last year, were adopted and accepted in their present form.

The Nominating Committee, composed of three members of the Board of Regents and three members of the College-at-large, nominated one candidate for each elective office three months before the ensuing election. A ballot election was held in open meeting with instructions that additional nominations could be made from the floor. The following officers were elected to serve for one-year terms, July 1, 1947, to July 1, 1948: President, Dr. Hal M. Davison, Atlanta, Georgia; President-Elect, Dr. George E. Rockwell, Milford, Ohio; First Vice President, Dr. J. Warrick Thomas, Richmond, Virginia; Second Vice President, Dr. Robert F. Hughes, Hamilton, Ontario, Canada. The members nominated and elected to serve for three-year terms, July 1, 1947 to July 1, 1950, on the Board of Regents were: Dr. Harold A. Abramson, New York, New York; Dr. Jonathan Forman, Columbus, Ohio; Dr. John H. Mitchell, Columbus, Ohio; and Dr. Albert V. Stoesser, Minneapolis, Minnesota.

Dr. Leon Unger, President, called attention to the services which have been rendered to the College by the retiring members of the Board since its inception. By virtue of his position as Secretary-Treasurer, the Board appointed Dr. Fred W. Wittich an ex-officio member of the Board of Regents.

The business session adjourned with the introduction of the new President, Dr. Hal M. Davison.

COMMITTEE FOR TESTING NEW AND UNUSED THERAPEUTICS

At the meeting of the Board of Regents at Atlantic City, June 6, the Committee for the Testing of New and Unused Therapeutics, Dr. Ethan Allan Brown, chairman, was reorganized. It is planned to notify all pharmaceutical concerns that the Committee is ready to consider the investigation of drugs applicable to the treatment of allergic conditions. Pilot tests are to be done on small groups of private and clinic patients by several physicians working independently, and thereafter by selected workers in geographically distributed centers. Physicians interested in group investigations of this type are invited to communicate with the chairman of the Committee, listing their qualifications and the facilities at their disposal. The results of such investigations will give due credit to all of the contributing members.

HONORARY FELLOWSHIPS

Dr. Marie B. Morrow, of the University of Texas, Department of Botany and Bacteriology, has been elected an Honorary Fellow of the American College of Allergists by reason of her meritorious contributions to research in allergy in relation to atmospheric molds.

Dr. Morrow is engaged full time in teaching and devotes most of her time to Mycology. Over a period of approximately fifteen years, she has been very actively interested in mold allergy and has done invaluable work in this field. This interest has enabled the Association of Allergists for Mycological Investigations to conduct its studies in the field of mold allergy since the inception of the organization in 1938.

* * *

Dr. Noble P. Sherwood, Professor of Bacteriology, School of Medicine, University of Kansas, has been elected an Honorary Fellow of the American College of Allergists, for his various contributions to research in allergy, immunology, and high attainments in the science of bacteriology.

One of the recent visitors to the headquarters of the College and of the International Association of Allergists was Dr. Zaida Eriksson-Lihr, Dr. Med. et Chir., Chief Physician of the Hospital for Allergic Diseases, Drumso, Finland. Dr. Eriksson is in charge of a new allergy hospital and clinic at Drumso.

The hospital was erected through private subscription. The library is greatly in need of literature, journals, and textbooks, on allergy, physiology, immunochemistry, et cetera. Any publications sent to the above address will be greatly appreciated.

At the regular meeting of the Chicago Society of Allergy, held on April 21, an election of officers was held and the following men were elected: Dr. Theodore B. Bernstein, President; Dr. Edward G. Tatge, President-Elect; Dr. Morris A. Kaplan, Secretary-Treasurer.

Any allergist wishing to secure a well-trained technician in the field of allergy, please contact the Secretary-Treasurer of the American College of Allergists, 423 LaSalle Medical Building, Minneapolis, Minnesota.

The Central Pennsylvania Allergy Association will hold its next annual meeting at Harrisburg, Pennsylvania, October 30, 1947. Dr. Stephen D. Lockey, Lancaster, Pennsylvania, is president, and Dr. Ralph Mulligan, Reading, Pennsylvania, is secretary.

In Memoriam

HARRY GUS GREDITZER, M.D., F.A.C.A.

We regret to announce the death of Dr. Harry Greditzer, September 27, 1946, at St. Louis, Missouri. He was born in Nevada, Missouri, December 4, 1889. After graduating from the Central High School in St. Louis in 1908 he attended Washington University School of Medicine from which he graduated in 1912. Dr. Greditzer interned at Washington University, was visiting surgeon at the St. Louis City Hospital, and assistant surgeon at the Maternity Hospital. He took post-graduate studies at St. Louis University in the Ear, Nose and Throat Clinic and later specialized as a Nose and Throat Allergist. He was an instructor in Urology at Washington University from 1914 to 1930. During World War I he was an instructor in Urology in the officers school there. He also held staff positions at the Children's Hospital, Jewish Hospital and St. Luke's Hospital, all of St. Louis.

Dr. Greditzer was a member of Phi Beta Pi, medical fraternity, and Alpha Omega Alpha. He was a member of the St. Luke's Medical Society, the Missouri State Medical Association, the American Medical Association, the American Urological Association, and the Southern Medical Association. He was a member of the medical staff of Washington University and assistant in surgery and surgeon to out-patients in the Genito-Urinary Department. He was elected a Fellow of the American College of Allergists in 1945.

Dr. Greditzer is survived by his wife, three sons, Harry G. Greditzer, Jr., David A., and Arthur S., and a grandson, Harry G. Greditzer, III.

The American College of Allergists is indeed sorry to lose this member of high standing, whose interest in the activities of the College has always been much appreciated.

ALLERTEEN By W. L. Mermis, M.D. The Tenth Series of Letters of the International Correspondence Club of Allergy, X—page 109.

This is the report of an eight-months-old baby with an eczema of the lower extremities. The baby had a similar dermatitis at the age of about three weeks which was treated by a pediatrician who placed her on a soybean formula. The baby, however, was unable to tolerate this milk because of frequent watery bowel movements.

The baby was then placed on a goat's milk formula which corrected the character of the stools and there were normal bowel movements. However, the eczema did not improve but became worse, involving at this time both arms.

The baby was immediately placed on Allerteen, a soybean milk preparation which did not cause loose stools, and there was marked improvement in the eczema. After two months on this preparation, the dermatitis disappeared and at no time did the baby object to taking this form of milk.

HORSE IMMUNOLOGY FOR ALLERGISTS

(Continued from Page 380)

globulin was obtainable on intravenous immunization; but the same antigen evoked non-precipitating antibodies upon subcutaneous treatment. It is pertinent that related observations were made in rabbits. They respond to the intradermal and subcutaneous introduction of pneumococci or streptococci with antibody versus the species-specific nucleoproteins rather than to the type-specific carbohydrates, whereas upon intravenous injections the inverse is true. The allergist would like to know more about the mechanisms involved in these findings, because he has so many difficulties in distinguishing between the modifying influence of the site of sensitization, and that of individual—that is genetically dominated—factors upon the type and manifestations of allergic disease.

ATOPIC CATARACT

(Continued from Page 363)

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